#17 Petition $200

BOX PATENT EXT. $

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 87147/395

In re: U.S. Patent No. 5,196,444

Patentee: Takehiko NAKA *et al.*

Issue Date: March 23, 1993

REQUEST FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. § 156

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Hiroshi Akimoto, Ph.D., agent for Takeda Chemical Industries Ltd., the owner of record of the above-identified patent, hereby requests an extension of the patent term of U.S. Patent No. 5,196,444.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740.

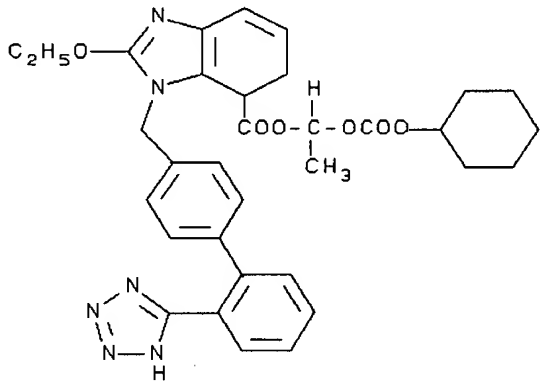
(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is a composition containing Candesartan Cilexetil (brand-name: ATACAND™).

Candesartan Cilexetil has:

(a) the chemical name 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate;

(b) the structural formula



(c) the empirical formula $C_{33}H_{34}N_6O_6$; and

(d) a molecular weight of 610.67.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review of the Candesartan Cilexetil product occurred under § 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 310 *et seq.* Section 505(b) provides for the submission and approval of new drug applications ("NDAs").

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

The product was approved by the FDA for commercial marketing and use for the treatment of hypertension pursuant to § 505(b) of the FFDCA on June 4, 1998. See Exhibit A.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved:

The approved product comprises the active ingredient Candesartan Cilexetil. Candesartan Cilexetil has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted:

The approved product was approved for commercial marketing and use on June 4, 1998. The last day within the sixty day period set forth in 37 C.F.R. § 1.720(f) therefore is August 3, 1998. The date of submission of the present application is on or before this date. The present application therefore has been timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No. 5,196,444
Inventors: Takehiko Naka, Kohei Nishikawa, Takeshi Kato
Issue Date: March 23, 1993
Expiration Date: April 18, 2011

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 5,196,444 is attached as Exhibit B.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

The receipt for the 3.5 year maintenance fee payment for U.S. Patent 5,196,444 is attached as Exhibit C.

A request for a Certificate of Correction was submitted October 5, 1995, to correct printing errors that were the fault of the Patent Office. Copies of the Request and Certificate are attached as Exhibit D.

No disclaimer or re-examination certificate has issued in connection with U.S. Patent No. 5,196,444.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product:

U.S. Patent 5,196,444 claims the approved product and a method of using the approved product.

Claim 1 of the patent recites a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate. The approved product comprises a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate; accordingly claim 1 reads on the approved product.

Claim 2 of the patent recites a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having specific lattice spacings. The approved product comprises a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having the lattice spacings recited in claim 2; accordingly, claim 2 reads on the approved product.

Claim 3 of the patent recites a pharmaceutical composition for antagonizing angiotensin II comprising a therapeutically effective amount of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, excipient, or diluent therefor. The approved product comprises a 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate in admixture with a pharmaceutically acceptable carrier, excipient, or diluent therefor; accordingly, claim 3 reads on the approved product.

Claim 4 recites a pharmaceutical composition comprising a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate in admixture with a pharmaceutically acceptable carrier, excipient, or diluent therefor. The approved product comprises a pharmaceutical composition comprising a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate in admixture with a pharmaceutically acceptable carrier, excipient, or diluent therefor; accordingly, claim 4 reads on the approved product.

Claim 5 recites a pharmaceutical composition comprising a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having specifically recited lattice spacings. The approved product comprises a pharmaceutical composition comprising a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having the lattice spacings recited in claim 5; accordingly, claim 5 reads on the claimed product.

Claim 6 of the patent recites a method for antagonizing angiotensin II in a mammal comprising administering a therapeutically effective amount of 1-(cyclohexyloxycarbonyloxy)-ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof. The approved product comprises 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate; accordingly, claim 6 reads on a method of using the approved product.

Claim 7 of the patent recites a method for antagonizing angiotensin II in a mammal comprising administering a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate. The approved product comprises a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate; accordingly, claim 7 reads on a method of using the approved product.

Claim 8 of the patent recites a method for antagonizing angiotensin II in a mammal comprising administering a therapeutically effective amount of a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having specific lattice spacings. The approved product comprises a stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate having the lattice spacingsrecited in claim 8; accordingly, claim 8 reads on a method of using the approved product.

Claim 9 of the patent recites 1-(cyclohexyloxycarbonyloxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof. The approved product comprises 1-

(cyclohexyloxycarbonyloxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate; accordingly, claim 9 reads on the approved product.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

> **(i) For a patent claiming a human drug, antibiotic or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued:**

On May 15, 1995, Astra Merck Inc. ("Astra Merck"), a licensee of U.S. Patent No. 5,196,444, submitted to the FDA an IND for the Candesartan Cilexetil product. See Exhibit E. The IND was assigned number IND 47,944 and became effective on May 16, 1995, thirty days after the date of receipt of the IND by the FDA. See Exhibit F. This establishes the beginning of the "regulatory review period" under 35 U.S.C. § 156(g)(1) as May 16, 1995 for Candesartan Cilexetil.

On April 30, 1997, Astra Merck submitted an NDA under § 505 of the FFDCA for the Candesartan Cilexetil product. A copy of the cover letter of April 30, 1997, accompanying the NDA is attached hereto as Exhibit G. The NDA was assigned number NDA 20,838.

The NDA for the Candesartan Cilexetil product was approved on June 4, 1998. Attached hereto as Exhibit A is a copy of the approval letter dated June 4, 1998, from the FDA to Astra Merck. Thus, for the purpose of determining the "regulatory review period" under 35 U.S.C. § 156(g)(1), June 4, 1998 is the date of the first approval of the product.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), Astra Merck submitted an IND for the approved product on May 15, 1995, and submitted an NDA for the approved product on April 30, 1997. Subsequent to the submission of the IND and NDA, Astra Merck had numerous contacts and meetings with the FDA with respect to the applications. These contacts and meetings are outlined in attached Exhibit H entitled "BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES DURING REGULATORY REVIEW PERIOD."

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension

35 U.S.C. § 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if the following requirements (1)-(5) are satisfied:

(1) the term of the patent has not expired before an application for extension is submitted.

The term of U.S. Patent No. 5,196,444, expires on April 18, 2011. This application has been submitted before the expiration of the patent term. Accordingly, this requirement is satisfied.

(2) the term of the patent has never been extended.

The term of U.S. Patent No. 5,196,444 never has been extended. Accordingly, this requirement is satisfied.

(3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d).

This application is submitted by an agent of the owner of record, Hiroshi Akimoto. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date that the approved product received permission for commercial marketing and use under the FFDCA and contains the information required under 35 U.S.C. § 156(d). Accordingly, this requirement is satisfied.

(4) the product has been subject to a regulatory review period before its commercial marketing or use.

As evidenced by the June 4, 1998, letter from the FDA (Exhibit A) the approved product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use. Accordingly, this requirement is satisfied.

> (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

The permission for the commercial marketing and use of the Candesartan Cilexetil product granted June 4, 1998, after regulatory review under § 505(b) of the FFDCA, is the first permitted commercial marketing or use of the product in the United States. Accordingly, this requirement is satisfied.

Because each of these requirements is satisfied, this patent is eligible for an extension.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 5,196,444 should be extended for 413 days, to June 4, 2012. This term of extension was determined on the following basis:

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

> (i) the length of time between the date an exemption under § 505(i) of the FFDCA became effective (the effective date of the IND) and the date an application was initially submitted under § 505 of the FFDCA (the date of the initial submission of the NDA)

The IND for the product was effective on May 16, 1995. The NDA for the product was submitted on April 30, 1997. Thus, for the purpose of this calculation, item (i) for the product equals the number of days from May 16, 1995 to April 30, 1997, or 715 days.

> (ii) the length of time between the date an application was initially submitted under § 505(b) of the FFDCA (the date of the initial submission of the NDA) and the date the application was approved (the approval date of the NDA).

The NDA for the product was submitted on April 30, 1997. The NDA was approved on June 4, 1998. Thus, for the purpose of this calculation, item (ii) equals the number of days from April 30, 1997 to June 4, 1998, or 400 days.

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. U.S. Patent No. 5,196,444 issued on March 23, 1993. The entire regulatory review period calculated above occurred after this issue date.

35 U.S.C. § 156(c) also sets forth the following exceptions (1)-(3) which may operate to shorten the length of the review period used to calculate patent term extension:

> (1) each period is reduced by any period during which the applicant did not act with due diligence.

In this case, there has been no lack of due diligence during the period of regulatory review calculated above. Accordingly, no reduction in the review period is required by this provision.

> (2) each period includes only one-half of the number of days in phase (i).

One-half of the number of days in phase (i) equals one-half of 715 days, or 357.5 days. Adding this number of days to the number of days in phase (ii) (400 days) results in a review period of 757.5 days, or 758 days.

> (3) if the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

On the date of approval of the product, June 4, 1998, 12 years and 318 days remained in the term of U.S. Patent No. 5,196,444. Adding this period to the review period calculated above yields a period of more than fourteen years. This provision, therefore, operates to shorten the period of extension to which U.S. Patent No. 5,196,444 is entitled. Accordingly, the extended term to which U.S. Patent No. 5,196,444 is entitled to under this provision expires fourteen years from the date of approval of the product, June 4, 2012.

35 U.S.C. § 1.56(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent 5,196,444 is April 18, 2011. Accordingly, the maximum extension allowed by this provision would extend the term to April 18, 2016. Extension of the patent by the number of days calculated above would not extend the patent beyond April 18, 2016. Accordingly, this provision does not operate to shorten the period of extension to which U.S. Patent No. 5,196,444 is entitled.

Thus, U.S. Patent 5,196,444 is entitled to an extension of 758 days, limited by provision (3) above. This means that the patent term should be extended for 413 days, to June 4, 2012.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought:

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension:

A check in the amount of $1,120 is enclosed with this application.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Patricia D. Granados
FOLEY & LARDNER
Washington Harbour, Suite 500
3000 K Street, N. W.
Washington, D. C. 20007-5109
TEL: (202) 672-5477
FAX: (202) 672-5399

(16) A duplicate of the application papers, certified as such:

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in 37 C.F.R. § 1.740(b):

DECLARATION

As agent for the owner of record of U.S. Patent 5,196,444 who has applied for an extension of the term of this patent, I declare that:

(1) I am an official of the corporate owner of U.S. Patent No. 5,196,444, authorized to obligate the corporation;

(2) I have reviewed and understand the contents of this application, which is submitted pursuant to 37 C.F.R. § 1.740 for extension of U.S. Patent 5,196,444;

(3) I believe that U.S. Patent 5,196,444 is subject to extension pursuant to 37 C.F.R. § 1.710;

(4) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) I believe that U.S. Patent 5,196,444, for which this extension is sought, meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,196,444.

July 7, 1998
Date

Hiroshi Akimoto, Ph.D.

A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-838

RECEIVED

JUN 0 4 1998

D. J. CUSHING, Ph.D.

JUN - 4 1998

Astra Merck Inc.
Attention: Daniel J. Cushing, Ph.D.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Dr. Cushing:

Please refer to your April 30, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atacand (candesartan cilexetil) 4, 8, 16, and 32 mg Tablets.

We acknowledge receipt of your submissions dated April 28, May 6, 8, 12, 18, 20 and 22 (two), 1998.

This new drug application provides for the use of Atacand (candesartan) Tablets in the treatment of hypertension.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed package insert included with your May 18, 1998 submission. Accordingly, the application is approved effective on the date of this letter.

We note that one of the May 22, 1998 submissions contains camera-ready proofs of carton and container labeling. Please submit 20 copies of the final printed carton and container labels as soon as they are available, in no case more than 30 days after they are printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-838. Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We note that the tentative dissolution specifications will be:

4 and 8 mg: Q of not less than 80% in 45 minutes
16 and 32 mg: Q of not less than 80% in 60 minutes

and you will monitor the dissolution of the first three batches of the 16 and 32 mg tablets placed on stability testing with the aim of revising the specifications for these strengths to Q of not less than 80% in 45 minutes.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Please submit one market package of the drug product when it is available.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

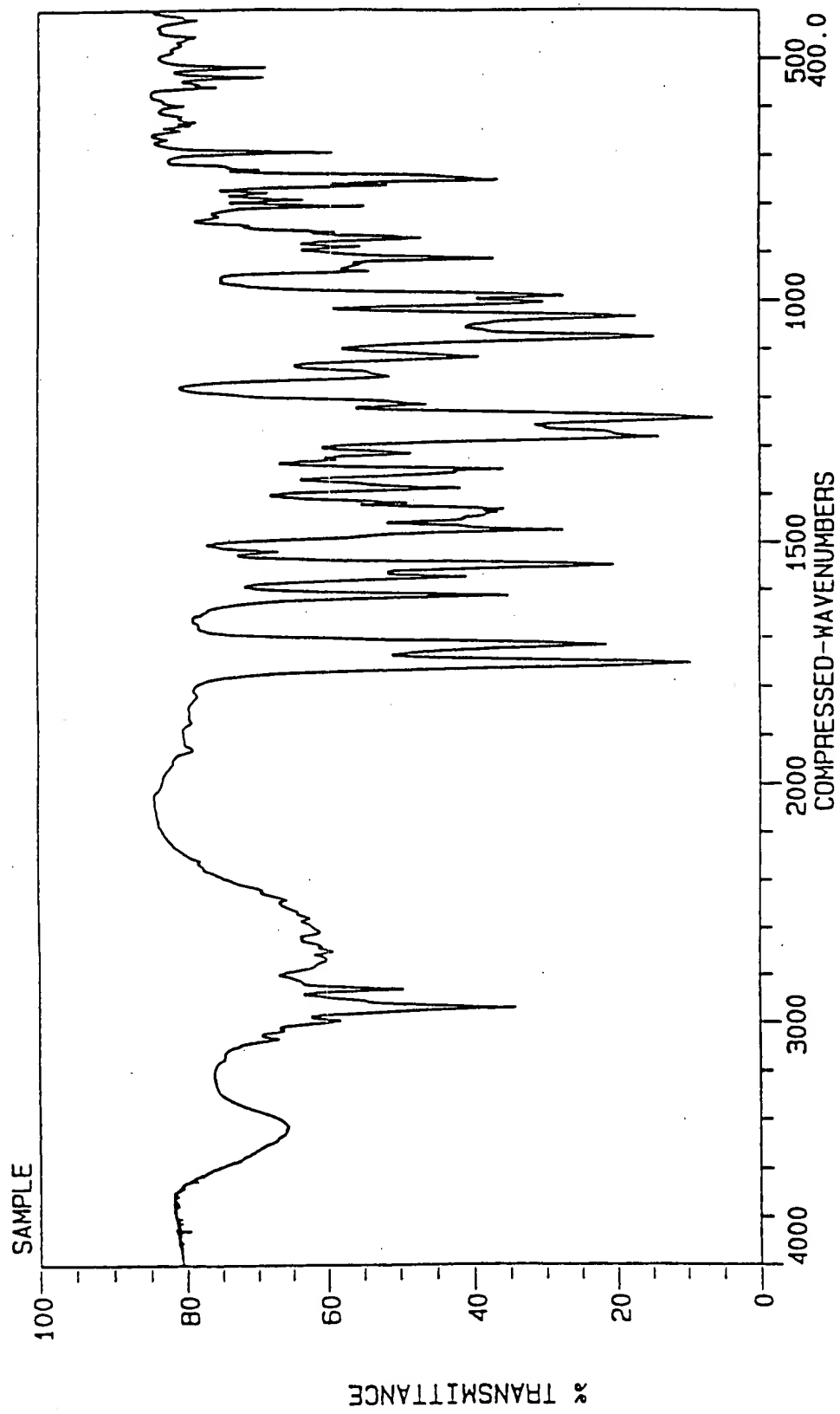

SAMPLE
100
80
60
40
20
0
% TRANSMITTANCE
4000
3000
2000
1500
1000
500
400.0
COMPRESSED-WAVENUMBERS

Figure 2

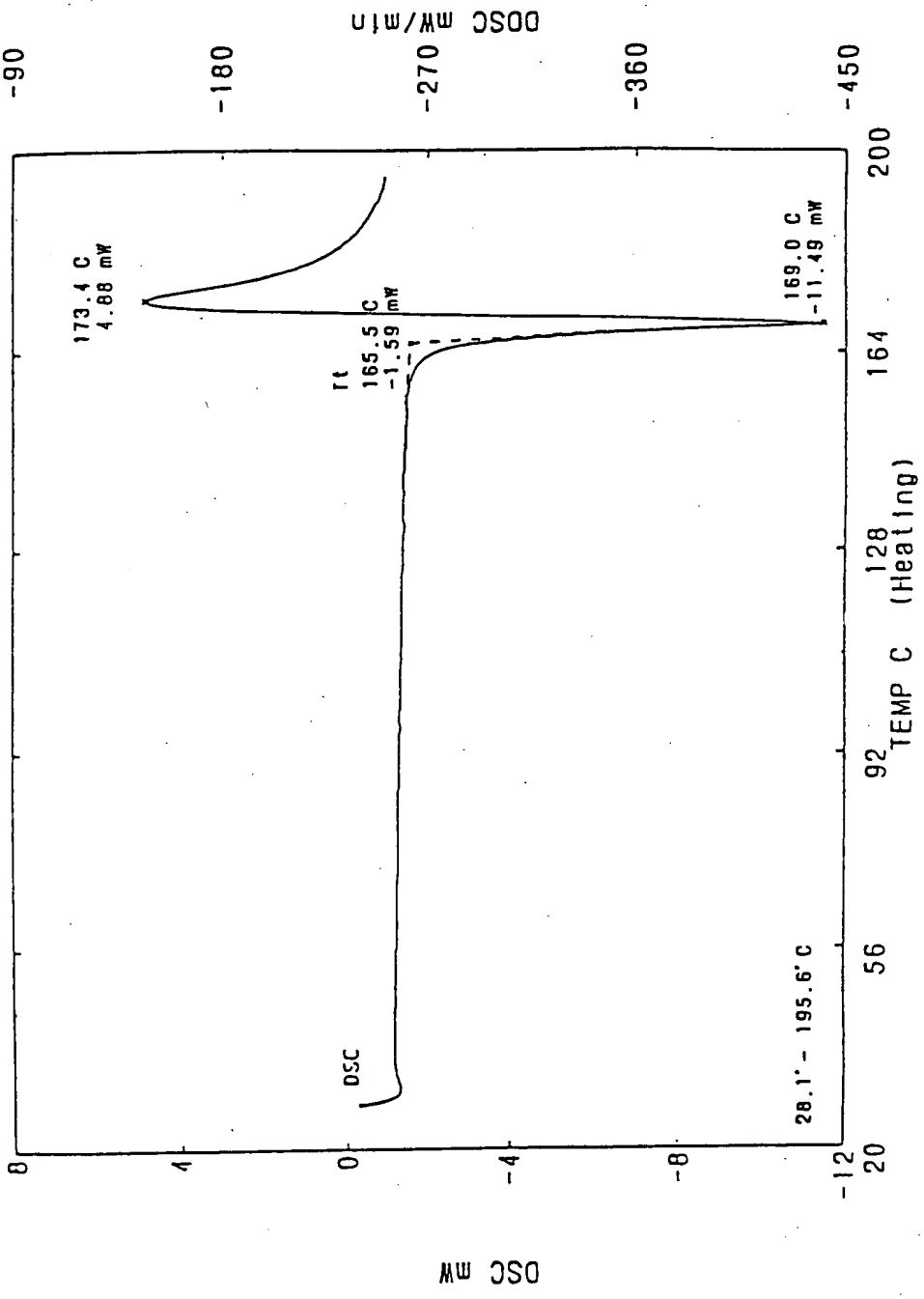

DDSC mW/min
-90
-180
-270
-360
-450
200
164
128
92
56
20
TEMP C (Heating)
173.4 C
4.88 mW
169.0 C
-11.49 mW
rt
165.5 C
-1.59 mW
DSC
28.1° - 195.6° C
8
4
0
-4
-8
-12
DSC mW

Figure 3

1-(CYCLOHEXYLOXYCARBONYLOXY)ETHYL 2-ETHOXY-1-[[2'-(1H-TETRAZOL-5-YL)BIPHENYL-4-YL]METHYL]BENZIMIDAZOLE-7-CARBOXYLATE AND COMPOSITIONS AND METHODS OF PHARMACEUTICAL USE THEREOF

SUMMARY OF THE INVENTION

In a first aspect of the invention there is provided 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate, including certain stable forms as well as pharmaceutically acceptable salts, which have

Potent anti-hypertensive activity and strong angiotensin II antagonistic action, which are of practical value in clinical use as therapeutic agents.

These compounds possess highly angiotensin II receptor antagonistic activity as well as exerting strong oral and long-lasting angiotensin II antagonistic and anti-hypertensive action.

These compounds are unexpectedly potent angiotensin II antagonists which are of value in the treatment of circulatory system diseases such as hypertensive diseases, heart diseases, strokes, nephritis, etc.

Another aspect of the present invention relates to pharmaceutical compositions comprising an effective amount of the 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate and a pharmaceutically acceptable carrier useful in treating circulatory system diseases such as hypertensive diseases, heart diseases, strokes, renal failure, nephritis, etc., and processes for preparing such compounds and compositions.

Still another aspect of the present invention relates to a method for treating said circulatory system diseases of animals, which comprises administering an effective amount of the 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate or the pharmaceutical composition thereof to said animal.

In a still further aspect of the invention, a method is provided for producing 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate which comprises contacting cyclohexyl 1-iodoethyl carbonate with 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid under conditions permitting esterification.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a X ray scattering chart obtained in Experimental Example 1.

FIG. 2 depicts an IR spectrum pattern obtained in Experimental Example 1.

FIG. 3 depicts a differential scanning calorimeter pattern obtained in Experimental Example 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate and the pharmaceutically acceptable salts thereof, which possess strong angiotensin II antagonist activity and are of value in the treatment of circulatory diseases such as hypertensive diseases, heart diseases, strokes, cerebral diseases, nephritis, etc., pharmaceutical compositions comprising an effective amount of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate and a pharmaceutically acceptable carrier useful in treating said circulatory diseases, and processes for preparing such compounds and compositions.

When the compounds of the present invention have several asymetric carbon atoms, they can thus exist in several stereochemical forms. The invention includes the mixture of isomers and the individual stereoisomers. It is intended that the present invention includes geometrical isomers, rotational isomers, enantiomers, racemates, and diastereomers.

Pharmaceutically acceptable salts of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate can be formed as salts with non-toxic, physiologically or pharmaceutically acceptable acids or bases, for example salts with an inorganic acid such as hydrochloride, sulfate or nitrate, and, depending on compounds, salts with an organic acid such as acetate, oxalate, succinate or maleate, salts with an alkali metal such as sodium salt or potassium salt, or salts with an alkaline earth metal such as calcium salt.

The compounds and the salts thereof thus produced are less toxic, strongly inhibit the vasoconstrictive and hypertensive actions of angiotension II, exert a hypotensive effect in animals, in particular mammals (e.g. human, dog, rabbit, rat, etc.), and therefore they are useful as therapeutics for not only hypertension but also circulatory diseases such as heart failure (hypertrophy of the heart, cardiac insufficiency, cardiac infarction or the like), strokes, cerebral apoplexy, nephropathy and nephritis. 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate and salts thereof according to the present invention strongly inhibit vasoconstriction and hypertension derived by angiotensin II and therefore possess potent anti-hypertensive activity in animals, more specifically mammal animals (e.g. humans, dogs, pigs, rabbits, rats, etc.). Further, 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate and salts thereof according to the present invention are of quite low toxicity and clinically useful in treating not only hypertension but also circulatory system diseases such as heart and brain diseases, strokes, renal failures, nephritis and the like.

For therapeutic use, 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate and salts thereof can be orally, parenterally, by inhalation spray, rectally, or topically administered as pharmaceutical compositions or formulations (e.g. powders, granules, tablets, pills, capsules, injections, syrups, emulsions, elixirs, suspensions, solutions and the like) comprising at least one such compound alone or in admixture with pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and/or diluents. The pharmaceutical compositions can be formulated in accordance with conventional methods. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intraperitoneal injections, or infusion techniques. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in water. Among the acceptable vehicles or solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil or fatty acid may be employed including natural, synthetic, or semi-synthetic fatty oils or acids, and natural, synthetic, or semi-synthetic mono-, di-, or triglycerides.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug. Solid dosage forms for oral administration may include powders, granules, tablets, pills, and capsules as mentioned above. In such solid dosage forms, the active compound may be admixed with at least one additive such as sucrose, lactose, celluloses, mannitol, maltitol, dextran, starches, agars, alginates, chitins, chitosans, pectins, tragacanth gums, arabic gums, gelatins, collagens, casein, albumin, and synthetic or semi-synthetic polymers or glycerides. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents as magnesium stearate, preservatives such as parabens and sorbic acid, antioxidants such as ascorbic acid, α-tocopherol and cysteine, disintegrants, binders, thickening, buffering, sweetening, flavoring, and perfuming agents. Tablets and pills can additionally be prepared with enteric coatings. Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, syrups, elixirs, suspensions, solutions containing inert diluents commonly used in the art, such as water.

Specific dose levels for any particular patient will be employed depending upon a variety of factors including the activity of specific compounds employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The dose varies with the diseases to be treated, symptoms, subjects and administration routes, and it is desirable that a daily dose of 1 to 50 mg for oral administration or 1 to 30 mg for intravenous injection can be administered in single or divided into 2 to 3 administrations when used as an agent for the therapy in adults. For example, when used for treating adult essential hypertension, the active ingredient will preferably be administered in an appropriate amount, for example, about 10 mg to 100 mg a day orally and about 5 mg to 50 mg a day intravenously. The active ingredient will preferably be administered in equal doses two or three times a day.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds.

EXAMPLES

By the following formulation examples, working examples, experimental examples and reference examples, the present invention will be explained more concretely, but they should not be interpreted as limiting the invention in any manner.

Examples of abbreviations in this specification are as follows:

Me: methyl, Et: ethyl, Tet: tetrazolyl, cycl: cyclo-, Pr: propyl, Bu: butyl, Pen: pentyl, Bu: butyl, Hex: hexyl, Hep: heptyl, Ph: phenyl, DMF: dimethylformamide, and THF: tetrahydrofuran.

FORMULATION EXAMPLES

When 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate of the present invention is used as a therapeutic agent for circulatory failures such as hypertension, heart diseases, strokes, kidney diseases, etc., it can be used in accordance with, for example, the following formulations.

1. Capsules

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate	10 mg
(2)	lactose	90 mg
(3)	fine crystalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

2. Tablets

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl] benzimidazole-7-carboxylate	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
	one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

REFERENCE EXAMPLE 1

Ethyl 2-carboxy-3-nitrobenzoate

A mixture of 3-nitrophthalic acid (35 g) in ethanol (300 ml) containing conc. sulfuric acid (20 ml) was heated under reflux for 24 hours. The solvent was evaporated in vacuo and the residue was poured into cold water (700 ml). The mixture was extracted with ethyl acetate. The organic layer was washed with water and shaken with an aqueous solution of potassium carbonate. The aqueous layer was made acidic with hydrochloric acid and the mixture was extracted with methylene chloride. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The resultant solid (29 g, 74%) was used for the subsequent reaction without purification.

^{1}H-NMR(90 MHz, $CDCl_3$) δ : 1.43(3H,t), 4.47(2H,q), 7.70(1H,t), 8.40(2H,d), 9.87(1H,br s)

IR(Nujol) cm^{-1}: 1725, 1535, 1350, 1300, 1270

REFERENCE EXAMPLE 2

Ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate

A mixture of ethyl 2-carboxy-3-nitrobenzoate (23.9 g) and thionyl chloride (12 ml) in benzene (150 ml) were

heated under reflux for 3 hours. The reaction mixture was concentrated to dryness. The resultant acid chloride (26 g, quantitative) was dissolved in methylene chloride (20 ml). The solution was added dropwise to a mixture of sodium azide (9.75 g) in dimethylformamide(DMF) (20 ml) with stirring vigorously. The reaction mixture was poured into a mixture of ether-hexane (3:1, 200 ml) and water (250 ml) to separate into two layers. The organic layer was washed with water, then dried, followed by evaporation of the solvent. The residue was dissolved in t-butanol (200 ml) and the solution was heated gradually with stirring, followed by heating under reflux for 2 hours. The reaction mixture was concentrated in vacuo to give an oily product (30 g).

^{1}H-NMR(90 MHz, $CDCl_3$) δ : 1.40(3H,t), 1.53(9H,s), 4.43(2H,q), 7.23(1H,t), 8.03–8.27(2H,m), 9.70(1H,br s)

IR(Neat) cm^{-1}: 3320, 2980, 1740, 1585, 1535, 1500, 1440, 1375, 1265, 1155

WORKING EXAMPLE 1

Ethyl 2-[[2'-cyanobiphenyl)]amino]-3-nitrobenzoate

To a solution of ethyl 2-t-butoxycarbonylamino-3-nitrobenzoate (20 g) in tetrahydrofuran (50 ml) was added, while stirring under ice-cooling, sodium hydride (60% dispersion in mineral oil, 2.8 g). The mixture was stirred at room temperature for 20 minutes and to the mixture were then added 4-(2-cyanophenyl)benzyl bromide (18 g) and potassium iodide (360 mg), followed by heating for 10 hours under reflux. The solvent was evaporated to dryness and the residue was partitioned between water (250 ml) and ether (200 ml). The organic layer was washed with water, dried and concentrated to give a yellow syrup. The syrup was dissolved in a mixture of trifluoroacetic acid (60 ml) and methylene chloride (40 ml) and the solution was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and to the residue was added ethyl ether (200 ml) to give crystals. The crystals were collected by filtration, washed with ether to give pale yellow crystals (22.1 g, 85%), m.p. 118°–119° C.

^{1}H-NMR(90 MHz, $CDCl_3$) δ : 1.37(3H,t), 4.23(2H,s), 4.37(2H,q), 6.37(1H,t), 7.33–7.83(9H,m), 7.97–8.20(2H,m)

IR(Nujol)cm^{-1}: 3280, 2220, 1690, 1575, 1530, 1480, 1450, 1255, 1105, 755

WORKING EXAMPLE 2

Ethyl
3-amino-2-[[2'-cyanobiphenyl-4-yl)methyl]amino]benzoate

To a solution of ethyl 2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]nitrobenzoate (10.4 g) in ethanol (50 ml) was added stannous dichloride dihydrate (28.1 g) and the mixture was stirred at 80° C. for two hours. The solvent was evaporated to dryness. To the ice-cooling mixture of the residue in ethyl acetate (300 ml) was added dropwise 2N NaOH (500 ml) with stirring. The aqueous layer was extracted with ethyl acetate (200 ml × 2). The organic layers were combined, washed with water, and dried. The solvent was evaporated to dryness and the residue was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate-hexane gave colorless crystals (7.3 g, 79%), m.p. 104°–105° C.

^{1}H-NMR(200 MHz, $CDCl_3$) δ : 1.33(3H,t), 4.23(2H,s), 4.27(2H,q), 6.83–6.93(2H,m), 7.35–7.55(7H,m), 7.64(1H,dt), 7.76(dd)

IR(KBr) cm^{-1}: 3445, 3350, 2220, 1680, 1470, 1280, 1240, 1185, 1160, 1070, 1050, 1020, 805, 750

WORKING EXAMPLE 3

Ethyl
1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate

Acetic acid (0.2 g) was added to a solution of ethyl 3-amino-2-N-[2'-cyanobiphenyl-4-yl)methyl]aminobenzoate (1.0 g) in ethyl orthocarbonate (5 ml). The mixture was stirred at 80° C. for one hour. The reaction mixture was concentrated, and the concentrate was dissolved in ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and water. The solvent was evaporated to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals (0.79 g, 69%), m.p. 131°–132° C.

Elemental Analysis for $C_{26}H_{23}N_3O_3$:	C (%)	H (%)	N (%)
Calcd.:	73.39;	5.45;	9.88
Found:	73.36;	5.42	9.83

^{1}H-NMR(200 MHz, $CDCl_3$) δ : 1.24(3H,t), 1.49(3H,t), 4.24(2H,q), 4.68(2H,q), 5.72(2H,s), 7.10(2H,d), 7.19(1H,t), 7.38–7.46(4H,m), 7.56–7.66(2H,m), 7.73–7.77(2H,m)

IR(KBr) cm^{-1}: 2220, 1720, 1550, 1480, 1430, 1280, 1245, 1215, 1040, 760, 740

WORKING EXAMPLE 4

Ethyl
2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]-methyl]benzimidazole-7-carboxylate

A mixture of ethyl 1-[(2'-cyanobiphenyl-4-yl)methyl]-2-ethoxybenzimidazole-7-carboxylate (0.7 g) and trimethyltin azide (0.7 g) in toluene (15 ml) was heated under reflux for 4 days. The reaction mixture was concentrated to dryness and to the residue were added methanol (20 ml) and 1N-HCl (10 ml). The mixture was stirred at room temperature for 30 minutes and adjusted to pH 3 to 4 with 1N NaOH. After removal of the solvent, the residue was partitioned between chloroform and water. The organic layer was washed with water and dried, and the solvent was evaporated to dryness to give a syrup. The syrup was purified by column chromatography on silica gel to give crystals. Recrystallization from ethyl acetate-benzene afforded colorless crystals (0.35 g, 45%), m.p. 158°–159° C.

Elemental Analysis for $C_{26}H_{24}N_6O_3$:	C (%)	H (%)	N (%)
Calcd.:	66.65;	5.16;	17.94
Found:	66.61;	5.05;	17.84

^{1}H-NMR(200 MHz,$CDCl_3$) δ : 1.09(3H,t), 1.43(3H,t), 4.02(2H,q), 4.30(2H,q), 5.57(2H,s), 6.71(2H,d), 6.83–6.96(4H,m), 7.27–7.31(1H,m), 7.40(1H,dd), 7.55–7.66(2H,m), 8.04–8.09(1H,m)

IR(KBr) cm^{-1}: 1720, 1605, 1540, 1470, 1430, 1250, 1040, 750

WORKING EXAMPLE 5

2-Ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylic acid

A solution of ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate (0.24 g) and 1N NaOH (1.5 ml) in ethanol (4 ml) was stirred at 80° C. for one hour. The reaction mixture was concentrated, and the concentrate was extracted with water and ethyl acetate. The aqueous layer was adjusted to pH 3-4 with 1N-HCl to give crystals. Recrystallization of the crystals from ethyl acetate-methanol afforded colorless crystals (0.15 g, 67%), m.p. 183°–185° C.

Elemental Analysis for $C_{24}H_{20}N_6O_3 \cdot 1/5H_2O$:			
	C (%)	H (%)	N (%)
Calcd.:	64.91;	4.63;	18.93
Found:	65.04;	4.51;	18.77

^{1}H-NMR(200 MHz,DMSO-d_6) δ : 1.38(3H,t), 4.58(2H,q), 5.63(2H,s), 6.97(4H,q), 7.17(1H,t), 7.47–7.68(6H,m)

IR(KBr) cm^{-1}: 1710, 1550, 1480, 1430, 1280, 1240, 1040, 760

WORKING EXAMPLE 6

2-Ethoxy-1-[[2'-(N-triphenylmethyltetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid

To a solution of 2-ethoxy-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (2.07 g) in methylene chloride (10 ml) were added trityl chloride (1.59 g) and triethylamine (0.8 ml). The mixture was stirred at room temperature for one hour. The reaction mixture was washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel to give crystals. Recrystallization of crude crystals thus obtained from ethyl acetate-benzene gave colorless crystals (2.12 g, 66%), m.p. 168°–170° C.

Elemental Analysis for $C_{43}H_{34}N_6O_3$:			
	C (%)	H (%)	N (%)
Calcd.:	75.64;	5.02;	12.31
Found:	75.37;	4.96;	12.20

^{1}H-NMR(200 MHz, $CDCl_3$) δ : 1.40(3H,t), 4.61(2H,q), 5.58(2H,s), 6.76(2H,d), 6.91–6.96(8H,m), 7.12(1H,t), 7.17–7.41(12H,m), 7.60(1H,dd), 7.73–7.82(2H,m)

WORKING EXAMPLE 7

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate

To a solution of 2-ethoxy-1-[[2'-(N-triphenylmethyl-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid (0.5 g) in DMF (5 ml) were added potassium carbonate (0.12 g) and cyclohexyl 1-iodoethyl carbonate (0.26 g). The mixture was stirred for one hour at room temperature. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried. After removal of the solvent, the residue was dissolved in methanol (10 ml) and to the solution was added 1N-HCl (2 ml). The mixture was stirred for one hour at room temperature. The reaction mixture was concentrated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water and dried. After removal of the solvent, the residue was purified by column chromatography on silica gel to give colorless powder (0.21 g, 47%), m.p. 103°–106° C.

Elemental Analysis for $C_{33}H_{34}N_6O_6$:			
	C (%)	H (%)	N (%)
Calcd.:	64.91;	5.61;	13.76
Found:	64.94;	5.71;	13.66

To the powder (1 g) obtained as above was added ethanol (6 ml). The mixture was stirred for 3 hours at room temperature and allowed to stand under ice-cooling. The mixture was then stirred for one hour at temperatures not higher than 10° C. Resultant crystals were collected by filtration and washed with cold ethanol. The crystals were dried at 25° C. for 9 hours under reduced pressure, then at 35° C. for further 18 hours to obtain white powdery crystals (0.94 g), m.p. 158°–166° C. (decomp.).

Elemental Analysis for $C_{33}H_{34}N_6O_6$:			
	C (%)	H (%)	N (%)
Calcd.:	64.91;	5.61;	13.76
Found:	64.73;	5.66;	13.64

^{1}H-NMR (200 MHz) δ : 1.13–1.84(16H,m), 4.28–4.55(3H,m), 5.65(2H,d), 6.72(1H,q), 6.81(2H,d), 6.93(2H,d), 7.03(1H,t), 7.22–7.23(1H,m), 7.31–7.36(1H,m), 7.52–7.60(3H,m), 8.02–8.07(1H,m)

IR(KBr) cm^{-1}: 2942, 1754, 1717, 1549, 1476, 1431, 1076, 1034, 750 MS(m/z): 611 $[M+H]^+$

EXPERIMENTAL EXAMPLE 1

Stable C-type crystalline 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate and preparation thereof

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate is usually purified by column chromatography on silica gel and the eluted fraction is concentrated to dryness to give amorphous powders. The powder is unstable by heat and impractical in production. For solving this problem, the present inventors made extensive experiments on crystallization of the subject compound and discovered C-type crystalline form. The C-type crystal is unexpectedly stable by heat and quite useful for production. The C-type crystal of the title compound has approximately the following lattice spacings:

3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle

5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak

IR spectrum (KBr tablet) of the C-type crystal is shown in FIG. 2 with the significant absorption maxima at 2942, 1754, 1717, 1615, 1549, 1476 and 750 cm^{-1} and its melting point is 158°–166° C. (decomposition). Representative X ray chart (powder method), IR spectra (KBr tablet) and differential scanning calorimeter patterns are shown in FIGS. 1–3, respectively.

The C-type crystal of 1-(cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate has advantages, for example;

1. It improves heat stability and practical utility.
2. Residual solvent can be minimized in crystals.
3. It can achieve industrial and clinical developments and give ecomomical benefits.

The concentrated residues, amorphous powders, and/or crystals except for the C-type crystal for obtaining the subject compound, are stirred in a suitable solvent to form the desired C-type crystal. In case where the C-type crystal is not formed, a small amount of the C-type crystal can be added as a seed to allow crystallization. Examples of such solvents are not limited to, as long as they afford the C-type crystal, but include lower alcohols (e.g. methanol, ethanol, isopropyl alcohol, etc.), a mixture of lower alcohol and water and a mixture of lower alkyl ketone (e.g. acetone, etc.) and water. Amounts of solvents used are not limited to, but practically, 2 to 30-fold per weight of the crystal. Ratios of lower alcohol vs. water and lower alkyl ketone vs. water are not limited to, but preferably 4:1 to 1:1. Stirring temperatures are not limited to, but −5° C. to 40° C., preferably 0° C. to 25° C.

EXPERIMENTAL EXAMPLE 2

Inhibition of binding of angiotensin II to angiotensin receptor

Method

An experiment of inhibition on the binding of angiotensin II (AII) to AII receptor was conducted by modifying the method of Douglas et al. [Endocrinology, 102, 685–696 (1978)]. An AII receptor membrane fraction was prepared from bovine adrenal cortex.

The compound of the present invention (10^{-6}M or 10^{-7}M) and ^{125}I-angiotensinII (^{125}I-AII) (1.85 kBq/50 μl) were added to the receptor membrane fraction, and the mixture was incubated at room temperature for one hour. The receptor-bound and free ^{125}I-AII were separated through a filter (Whatman GF/B filter), and the radioactivity of ^{125}I-AII bound to the receptor was measured.

Results

The results relating to the compounds of the present invention are shown in Table 2.

EXPERIMENTAL EXAMPLE 3

Inhibitory effect of the compound of the present invention on pressor action of AII

Method

Jcl: SD rats (9 week old, male) were employed. On the previous day of the experiment, these animals were applied with cannulation into the femoral artery and vein under anesthesia with pentobarbital Na. The animals were fasted but allowed to access freely to drinking water until the experiment was started. Just on the day of conducting the experiment, the artery cannula was connected with a blood-pressure transducer, and the average blood pressure was recorded by means of polygraph. Before administration of the drug, the pressor action due to intravenous administration of AII (100 ng/kg) as the control was measured. The drugs were orally administered, then, at each point of the measurement, AII was administered intravenously, and the pressor action was similarly measured. By comparing the pressor action before and after administration of the drug, the percent inhibition by the drug on AII-induced pressor action was evaluated.

Results

The results relating to the compounds of the present invention are shown in Table 2.

TABLE 2

Working Example No.	Radioreceptor Assay 1×10^{-7} M	Radioreceptor Assay 1×10^{-6} M	Pressor Response to A II (p.o.) 3 mg/kg
4	46	82	+++ a)
5	61	91	+++
7	32	77	+++

a) +++ ≧ 70% > ++ ≧ 50% > + ≧ 30% > −

The foregoing is merely illustrative of the invention and is not intended as limiting the scope of the invention which is defined by the following claims:

What is claimed is:

1. A stable crystal of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylate.

2. A stable crystal according to claim 1, which has approximately the following lattice spacings:

3.5 angstrom; middle
3.7 angstrom; weak
3.8 angstrom; middle
4.0 angstrom; middle
4.1 angstrom; weak
4.3 angstrom; weak
4.4 angstrom; middle
4.6 angstrom; middle
4.8 angstrom; middle
5.1 angstrom; middle
5.2 angstrom; weak
6.9 angstrom; weak
7.6 angstrom; weak
8.8 angstrom; middle
9.0 angstrom; strong
15.9 angstrom; weak.

3. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier, excipient or diluent therefor.

4. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a crystal according to claim 1 in admixture with a pharmaceutically acceptable carrier, excipient or diluent therefor.

5. A pharmaceutical composition for antagonizing angiotensin II which comprises a therapeutically effective amount of a crystal according to claim 2 in admix-

ture with a pharmaceutically acceptable carrier, excipient or diluent therefor.

6. A method for antagonizing angiotensin II in a mammal which comprises administering to said mammal a therapeutically effective amount of 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

7. A method for antagonizing angiotensin II in a mammal which comprises administering to said mammal a therapeutically effective amount of a crystal according to claim 1.

8. A method for antagonizing angiotensin II in a mammal which comprises administering to said mammal a therapeutically effective amount of a crystal according to claim 2.

9. 1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof.

* * * * *

United States Patent [19]
Naka et al.

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[54] 1-(CYCLOHEXYLOXYCARBONYLOXY)ETHYL 2-ETHOXY-1-[[2'-(1H-TETRAZOL-5-YL)BIPHENYL-4-YL]METHYL]BENZIMIDAZOLE-7-CARBOXYLATE AND COMPOSITIONS AND METHODS OF PHARMACEUTICAL USE THEREOF

[75] Inventors: **Takehiko Naka**, Kobe; **Kohei Nishikawa**, Kyoto; **Takeshi Kato**, Higashiosaka, all of Japan

[73] Assignee: **Takeda Chemical Industries, Ltd.**, Osaka, Japan

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Aug. 6, 1990	[JP]	Japan	2-208662
Oct. 1, 1990	[JP]	Japan	2-264579
Dec. 24, 1990	[JP]	Japan	2-413679

[51] **Int. Cl.**[5] **C07D 257/04**; A61K 31/41
[52] **U.S. Cl.** **514/381**; 548/253; 548/252
[58] **Field of Search** 514/381; 548/253

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,526,896	7/1985	Schevrel et al.	548/253
4,764,623	8/1988	Kees	548/253
4,775,679	6/1988	Chang	548/253
4,880,804	11/1989	Carini et al.	514/381

FOREIGN PATENT DOCUMENTS

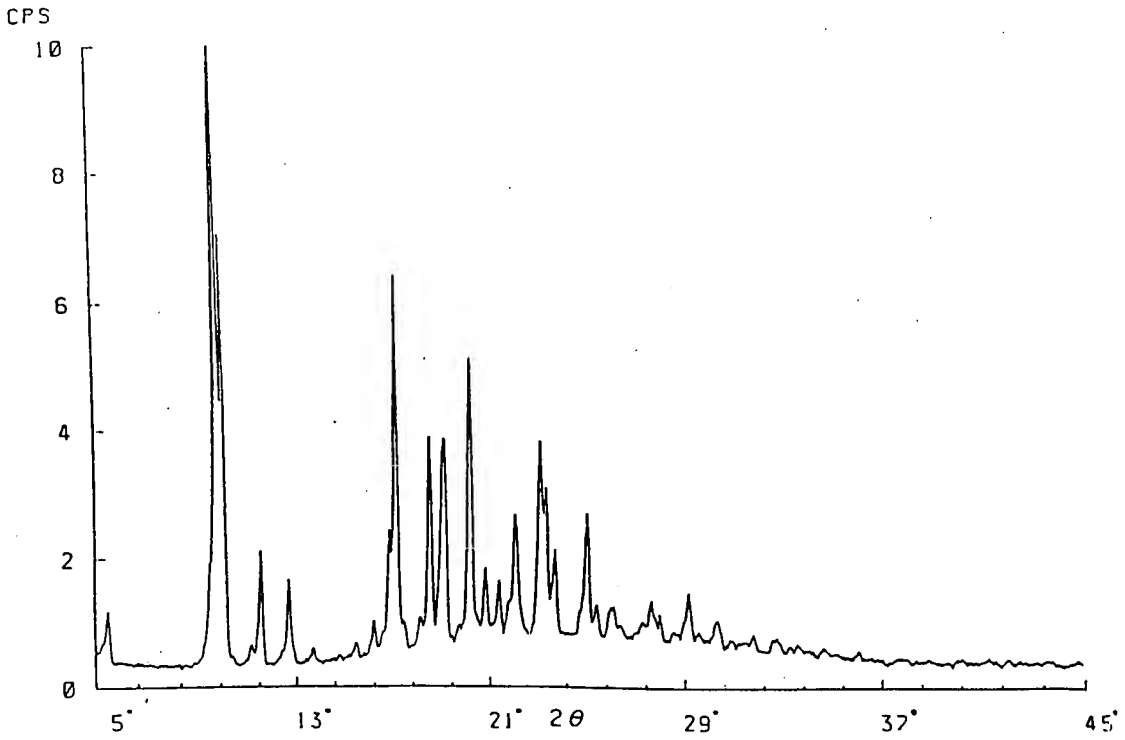
0028833	5/1981	European Pat. Off. .
0028834	5/1981	European Pat. Off. .
0245637	11/1987	European Pat. Off. .
0253310	1/1988	European Pat. Off. .
0291969	11/1988	European Pat. Off. .
0323841	7/1989	European Pat. Off. .
0392317	10/1990	European Pat. Off. .
0400835	12/1990	European Pat. Off. .

Primary Examiner—David B. Springer
Attorney, Agent, or Firm—Wegner, Cantor, Mueller & Player

[57] **ABSTRACT**

1-(Cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate or a pharmaceutically acceptable salt thereof has potent angiotensin II antihypertensive activity, thus being useful as therapeutic agents for treating circulatory system diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, nephritis, etc.

9 Claims, 3 Drawing Sheets



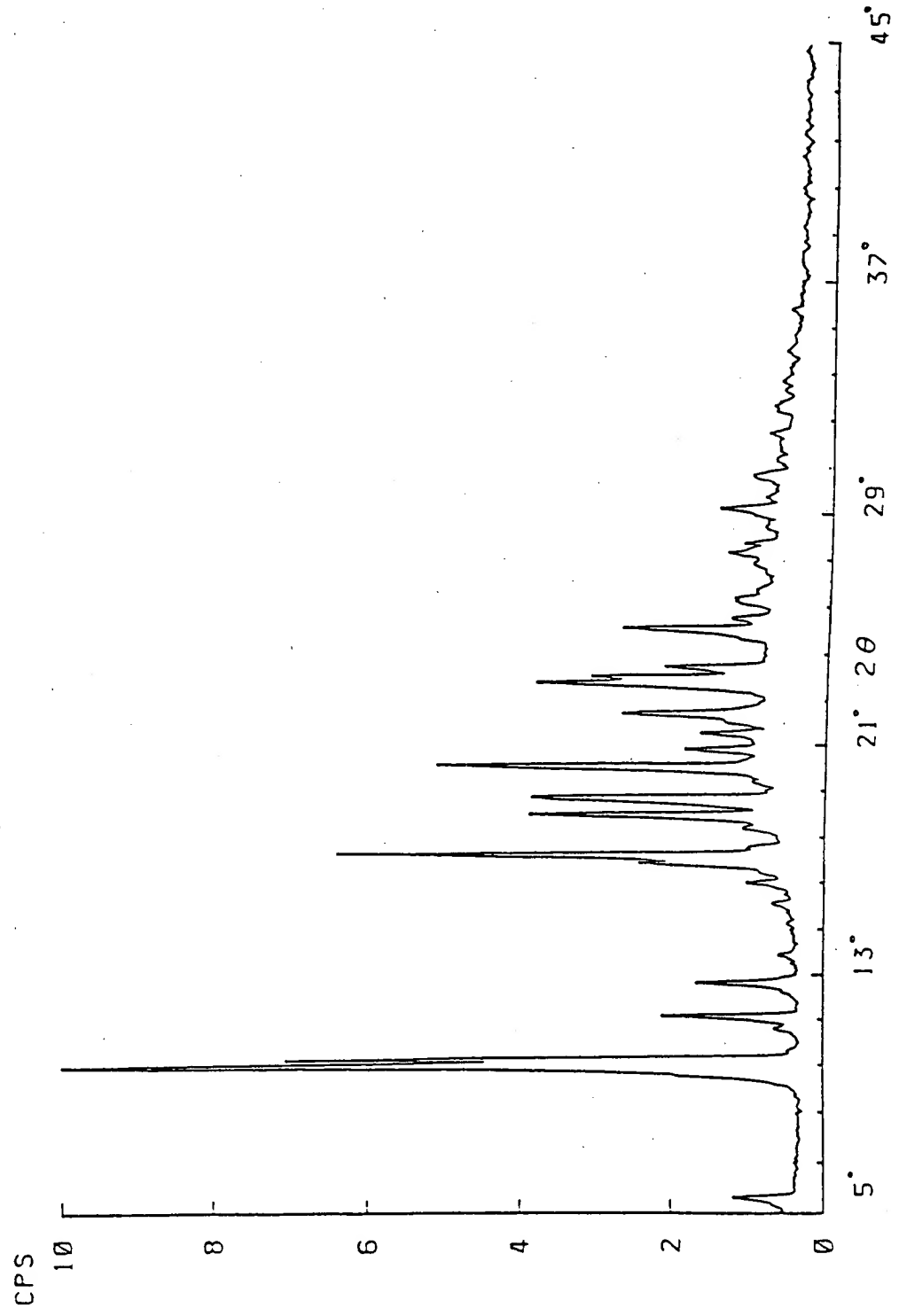


Figure 1

Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

C

75N5/0916

FOLEY & LARDNER
3000 K STREET, N.W.
SUITE 500
WASHINGTON, D.C. 20007-5109

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,196,444	183	990	----	07/687,238	03/23/93	04/18/91	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	P-4414-22823

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, DC 20231

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of
Takehiko NAKA et al.
Patent No. 5,196,444
Issued: March 23, 1993

Date Allowed: Feb. 25, 1992
Batch No.: A48
Serial No. 07/687,238
Filed: April 18, 1991

For: 1-(CYCLOHEXYLOXYCARBONYLOX-YETHYL 2-ETHOXY-1-[[2'-(1H-TETRAZOL-5-YL)BIPHENYL-4-YL]METHYL]BENZIMIDAZOLE-7-CARBOXYLATE AND COMPOSITIONS AND METHODS OF PHARMACEUTICAL USE THEREOF

REQUEST FOR CERTIFICATE OF
CORRECTION UNDER 37 C.F.R. §1.322

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Patentee hereby respectfully requests the Commissioner to issue a Certificate of Correction for the above-captioned patent in accordance with the accompanying Form PTO-1050 (submitted in duplicate).

In Column 4, between lines 44 and 45, please insert the following:

--3. Injections

(1)	2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid disodium salt		10 mg
(2)	inositol		100 mg
(3)	benzyl alcohol		20 mg
		one ampoule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.

4. Capsules

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate	10 mg
(2)	lactose	90 mg
(3)	fine crysatalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

5. Tablets

(1)	1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
	one tablet	230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

6. Injections

(1)	2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid disodium salt	10 mg
(2)	inositol	100 mg
(3)	benzyl alcohol	20 mg
	one ampoule	130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.--

Since this Certificate is needed to correct the mistakes which were the fault of the Patent and Trademark Office, it is believed that no fee is required.

Respectfully submitted,

October 5, 1995
Date

Harold C. Wegner
Reg. No. 25,258

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109
Tel: (202) 672-5300

Staple Here Only 1

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,196,444
DATED : March 23, 1993
INVENTOR(S) : Takehiko NAKA et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

In Column 4, between lines 44 and 45, please insert the following:

-- 3. Injections

(1) 2-methylthio-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid disodium salt 10 mg

(2) inositol 100 mg

(3) benzyl alcohol 20 mg

one ampoule 130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.

MAILING ADDRESS OF SENDER:
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PATENT NO. 5,196,444

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FORM PTO 1050 (Rev. 2-93)

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,196,444
DATED : March 23, 1993
INVENTOR(S) : Takehiko NAKA et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

4. Capsules

(1)	1-(cyclohexyloxycarbonyloxy)ethyl2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate	10 mg
(2)	lactose	90 mg
(3)	fine crysatalline cellulose	70 mg
(4)	magnesium stearate	10 mg
	one capsule	180 mg

(1), (2), (3) and a half of (4) are mixed and granulated. To the granules is added the remainder of (4), and the whole is filled into gelatin capsules.

5. Tablets

(1)	1-(cyclohexyloxycarbonyloxy)ethyl2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylate	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	fine crystalline cellulose	30 mg

MAILING ADDRESS OF SENDER:
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PATENT NO. 5,196,444

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PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,196,444
DATED : March 23, 1993
INVENTOR(S) : Takehiko NAKA et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

(5) magnesium stearate 5 mg

one tablet 230 mg

(1), (2), (3), two thirds of (4) and a half of (5) are mixed and granulated. To the granules are added the remainders of (4) and (5), followed by subjecting the granules to compression molding.

6. Injections

(1) 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]benzimidazole-7-carboxylic acid disodium salt 10 mg

(2) inositol 100 mg

(3) benzyl alcohol 20 mg

one ampoule 130 mg

(1), (2) and (3) are dissolved in distilled water for injection to make the whole volume 2 ml, which is filled into an ampoule. The whole process is conducted under sterile conditions.--

MAILING ADDRESS OF SENDER:
FOLEY & LARDNER
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Washington, DC 20007-5109

PATENT NO. 5,196,444

No. of add'l copies @ 50¢ per page

FORM PTO 1050 (Rev. 2-93)

E

ELLIOTT T. BERGER, Ph.D.
Executive Director, Regulatory Affairs

ASTRA MERCK

725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1057
Fax 610 889-1292

May 15, 1995

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110
Central Document Room
Center for Drug Evaluation & Research
Food and Drug Administration
Park Buildings, Room 214
12420 Parklawn Drive
Rockville, MD 20852

Serial No. 000

Dear Dr. Lipicky:

Original IND: Candesartan cilexetil

In accordance with Section 505(i) of the Food, Drug and Cosmetic Act, and Section 312.1 of Title 21 of the Code of Federal Regulations, we are submitting with this letter an Investigational New Drug Application for Candesartan cilexetil Tablets.

Candesartan cilexetil was developed by Takeda Chemical Industries Ltd., Japan as an AT_1 subtype-selective angiotensin II receptor antagonist. Candesartan cilexetil is also known as TCV-116. According to an agreement between Takeda and AB Astra, Sweden, both companies will be engaged in the worldwide clinical development and future marketing of the drug. AB Astra has designated Astra Merck Inc. for the clinical development of candesartan cilexetil within the United States.

Candesartan cilexetil is to be initially investigated for the treatment of hypertension. Based on the European and Japanese data contained and summarized within this application, we will initiate a Phase III clinical program for the treatment of hypertension with candesartan cilexetil.

We have tentatively scheduled an End-of-Phase II conference for June 22 and 23, 1995 to review the preclinical toxicology (June 22) and clinical programs (June 23) for candesartan cilexetil to insure that these programs will

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satisfactorily fulfill FDA requirements. Background documentation for these meetings will be provided in the near future. We will contact your office shortly to confirm this meeting.

We consider the fact of filing this Investigational New Drug Application to be confidential matter, and respectfully request the Food and Drug Administration not to make its existence public without first obtaining the permission of Astra Merck Inc. In addition, we regard the portions of this Application specified below as methods or processes constituting trade secrets, or privileged or confidential information and entitled to the protection of section 301(j) of the Food, Drug and Cosmetic Act, Section 552 of Freedom of Information Act and other relevant statutes and regulations.

1. Chemistry, Manufacturing and Control Information contained in, or referenced in, Section 7 of this Application.

2. Nonclinical Pharmacology and Toxicology Information contained in Section 8 of this Application.

3. Clinical plans for studies of the drug in humans contained in Sections 3 through 6 of this Application. Please note that we do not intend to initiate the clinical trial described in this Application until after the above mentioned End of Phase II Conferences.

Questions concerning this submission should be addressed to Elliott T. Berger, Ph.D. (610/695-1057), or in my absence, to Daniel J. Cushing, Ph.D. (610/695-1370).

Sincerely,

Elliott T. Berger, Ph.D.
Executive Director
Regulatory Affairs

Attachment

Federal Express Tracking No. 2478597995

F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 47,944

MAY 18 1995

Astra Merck Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Dear Sir/Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying information:

IND Number Assigned: 47,944

Sponsor: Astra Merck Inc.

Name of Drug: Candesartan cilexetil

Date of Submission: May 15, 1995

Date of Receipt: May 16, 1995

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30-day period, we determine that serious deficiencies in your IND require correction before human studies can begin or that would require restriction of human studies until correction, we will notify you immediately by telephone. In that event, we expect that you will withhold or restrict such studies until we notify you that the material you have submitted to correct the deficiencies is satisfactory.

A sponsor of an IND may obtain supplies of the investigational drug upon notification of our receipt of the application. Sponsors, however, may not ship the investigational drug to investigators named in the IND until 30 days after the receipt date.

The 30-day restriction does not apply if the IND number was assigned for emergency use of the drug.

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You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act. These responsibilities include reporting any unexpected fatal or life-threatening experience to us by telephone no later than three working days after receipt of the information, reporting adverse reactions that are both serious and unexpected in writing within ten days and submitting progress reports at least annually.

Please forward all future communications concerning this IND in TRIPLICATE, IDENTIFIED WITH THE IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane, HFD-110
Rockville, MD 20857

Should you have any questions concerning this IND, please call:

Kathleen Bongiovanni
Consumer Safety Officer
(301) 443-4730

Sincerely Yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I

cc: Original File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

6

DANIEL J. CUSHING, Ph.D., F.C.P.
Director, Regulatory Liaison

ASTRA MERCK
725 Chesterbrook Blvd.
Wayne, PA 19087-5677
610 695-1370
Fax 610 695-1828

April 30, 1997

Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Rockville, MD 20852

Dear Dr. Lipicky:

NDA 20-838
ATACAND™ (candesartan cilexetil) Tablets
Original New Drug Application

In accordance with 21 CFR 314, and section 505(b) of the Federal Food, Drug and Cosmetic Act, Astra Merck Inc. is submitting an Original New Drug Application for ATACAND™ (candesartan cilexetil) Tablets for the treatment of hypertension.

This Original New Drug Application consists of data from a clinical program conducted under IND 47,944 and from several clinical trials in hypertensive patients and in normal subjects conducted outside the U.S. by Takeda Chemical Industries, Ltd. and Astra Hässle AB. The safety and efficacy of candesartan cilexetil in the treatment of hypertension are supported by four (4) primary controlled clinical trials and several other controlled and uncontrolled clinical trials. The safety profile of candesartan cilexetil is further supported by a full analysis of safety data from all clinical trials and a complete list of all known deaths and non-fatal serious adverse events residing in the safety databases of Takeda Chemical Industries, Ltd., Astra Hässle AB and Astra Merck Inc.

Candesartan cilexetil is also under development in combination with hydrochlorothiazide for the treatment of hypertension under IND 50,491 and for the treatment of congestive heart failure under IND 50,115.

This application is formatted in accordance with 21 CFR 314.50. This application consists of an "archival" copy (blue binder) which consists of 259 printed volumes. We have also included five review copies. Each review copy includes administrative documentation, an overall Index to the Contents of the Application (Item 1), the Synopsis of the Application (Item 2) and the specific technical items as listed below.

Item 3 Chemistry, Manufacturing and Controls
(red binder) - 7 volumes

Item 4 Samples and Labeling
(red binder) - 2 volume

Item 5 Nonclinical Pharmacology and Toxicology Documentation
(yellow binder) - 31 volumes

Item 6 Human Pharmacokinetics and Bioavailability Documentation
(orange binder) - 24 volumes

Item 8 Clinical Documentation
(light brown binder) - 126 volumes

Item 10 Statistical Documentation
(green binder) - 74 volumes

FDA correspondence dated February 20, 1997 granted a waiver allowing for submission of NDA Items 11 and 12 in electronic format only and not as a paper submission. Subsequently, in FDA correspondence dated March 12, 1997, a waiver was granted for the omission of Item 11 entirely since the same information will be provided as full data sets from the world wide clinical database in SAS transport format. In total this NDA consists of 498 volumes, 259 of which are provided as printed volumes and the remaining 239 volumes are provided as the electronic version of Item 12.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No. 225847), in the amount of $102,500 was sent to the Food and Drug Administration, Pittsburgh, PA in correspondence dated March 21, 1997.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that in connection with this application, Astra Merck Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

In accordance with 21 CFR 314.50(j), we are hereby claiming exclusivity. Since candesartan cilexetil has not previously been approved under section 505(b) of the Act, we hereby reference 314.108 (b)(2) to support the exclusivity claim.

Documentation is on file that indicates original subject records were reviewed during the course of monitoring activities for verification of case report forms for all controlled clinical studies. In addition, all international studies were performed in accordance with the directives stated in the Declaration of Helsinki.

We consider the submission of this information to be confidential and proprietary and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Astra Merck Inc.

We are also providing a full copy of the Chemistry, Manufacturing and Controls Technical Section and Methods Validation Section (Items 3 and 4, respectively) to the Philadelphia District Office of the Food and Drug Administration.

If you have any questions or require any additional information concerning this Original New Drug Application please contact me directly at (610/695-1370) or, in my absence, Donald F. Dwyer, RAC, Regulatory Project Manager at (610/695-1291).

Sincerely yours,

Daniel J. Cushing, Ph.D.
Director
Regulatory Liaison

Enclosures
Hand Delivery

Desk Copy: Ms. Mary Ann Holovac, Drug Information Services, HFD-85, Rm 8B-37
(letter/patent information only)

Ms. Kathleen Bongiovanni, RHPM, HFD-110, letter only

BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES
DURING REGULATORY REVIEW PERIOD.

Date	Submission Type/Correspondence	To:	From:
11/12/96	Telephone Contact	AMI: Dan Cushing	FDA: Ms. K. Bongiovanni Dr. F. Zielinski
1/21/97	General Correspondence: IND 47,944	FDA: Dr. Lipicky	AMI:Dan Cushing
1/27/97	Telephone Contact	AMI:Dan Cushing	FDA:K. Bongiovanni
1/29/97	Telephone Contact	AMI:Don Dwyer	FDA:A. Elhage
2/3/97	Telephone Contact	FDA: Jeanna Johnson	AMI: Don Dwyer
3/21/97	General Correspondence	FDA	AMI: Marjorie Christie
4/30/97	General Correspondence	FDA: Dr. Lipicky	AMI: Marjorie Christie for Dan Cushing
4/30/97	Original NDA	FDA: Dr. Lipicky	AMI: Dan Cushing
5/7/97	General Correspondence	FDA: Ms. K. Bongiovanni	AMI:Dan Cushing
5/9/97	General Correspondence	AMI: Dan Cushing	FDA: Ms. K. Bongiovanni
6/3/97	Telephone Contact	AMI: Don Dwyer	FDA: Ms. K. Bongiovanni
6/4/97	Telephone Contact	AMI: Don Dwyer	FDA: Ms. K. Bongiovanni
6/4/97	Telephone Contact	AMI: Don Dwyer	FDA: Dr. Piechocki
6/12/97	Telephone Contact	AMI: Dan Cushing	FDA: Dr. Piechocki
6/27/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
7/15/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
7/15/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
7/22/97	Telephone Contact	FDA: Dr. Fredd	AMI: Dan Cushing
7/24/97	Telephone Contact	AMI:Robert Cobuzzi	FDA: Dr. Ahmed El Tahtawy
7/25/97	Telephone Contact	AMI:Dan Cushing trans. to: Robert Cobuzzi/ Terry Flanagan	FDA:Dr. Steve Caras

Date	Submission Type/Correspondence	To:	From:
7/28/97	Telephone Contact	AMI:Robert Cobuzzi/ Terry Flanagan	FDA:Dr. Steve Caras
7/29/97	General Correspondence	FDA: Dr. Lipicky	AMI: Dan Cushing
7/31/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
8/1/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
8/4/97	Telephone Contact	AMI:Cindy Lancaster	FDA:Dr. Anthony Proakis
8/4/97	General Correspondence	FDA: Dr. Lipicky	AMI: Dan Cushing
8/5/97	Telephone Contact	FDA:Dr. Jason Gross	AMI:Joanne Curley
8/5/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bonglovanni
8/5/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bonglovanni
8/7/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bonglovanni
8/11/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
8/12/97	Telephone Contact	FDA:Dr. Anthony Proakis	AMI:Mike Elia
8/12/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bonglovanni
8/12/97	Telephone Contact	AMI:Jeff Walker/Harish Bevinahally	FDA:Gloria Carandang (Cardio Renal)
8/12/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
8/13/97	Telephone Contact	AMI:Dan Cushing/ Terry Flanagan	FDA:Dr. Stephen B. Fredd
08/14/1997			
08/15/1997			
08/16/1997	Telephone Contacts	AMI:Cindy Lancaster/ Terry Flanagan	FDA:Dr. Stephen B. Fredd

Date	Submission Type/Correspondence	To:	From:
8/20/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bongiovanni
8/22/97	Telephone Contact	AMI:Dan Cushing/ Joanne Curley	FDA:Dr. Joseph Piechocki
8/22/97	Amendment to a Pending Application	FDA: Dr.Lipicky	AMI: Dan Cushing
8/25/97	FAX	FDA	AMI: Dan Cushing
8/26/97	Amendment to a Pending Application	FDA: Dr.Lipicky	AMI: Dan Cushing
8/26/97	Amendment to a Pending Application	FDA: Dr.Lipicky	AMI: Dan Cushing
8/27/97	Amendment to a Pending Application	FDA: Dr.Lipicky	AMI: Dan Cushing
8/28/97	Telephone Contact	FDA:Ms. K. Bongiovanni	AMI:Dan Cushing
8/29/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
8/29/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI: Dan Cushing
9/4/97	Telephone Contact	FDA:Dr. Stephen B. Fredd	AMI:Cindy Lancaster
9/4/97	Telephone Contact	FDA:Ms. K. Bongiovanni	AMI:Cindy Lancaster
9/5/97	Telephone Contact	AMI:Cindy Lancaster	FDA:Ms. K. Bongiovanni
9/5/97	Amendment to a Pending Application	FDA: Dr.Lipicky	AMI: Dan Cushing
9/6/97	FAX	FDA: Dr. Fredd Dr. Khin M. U	AMI: Cindy Lancaster CC: Dan Cushing
9/9/97	Telephone Contact	AMI:Dan Cushing	FDA:Dr. Stephen B. Fredd
9/15/97	Telephone Contact	AMI:Jeff Walker	FDA:Gloria Carandang (Cardio Renal)

Date	Submission Type/Correspondence	To:	From:
9/17/97 09/17/1997	Telephone Contact	FDA:Ms. K. Bongiovanni AMI:Cindy Lancaster (K.Bongiovanni returned Cindy Lancaster's call)	AMI:Cindy Lancaster FDA:Ms. K. Bongiovanni (K.Bongiovanni returned Cindy Lancaster's call)
09/19/1997	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bongiovanni
9/18/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
9/19/97	Telephone Contact	AMI:Dan Cushing	FDA:Dr. K. U
9/25/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
9/26/97	FDA Letter Request	AMI:Dan Cushing	FDA: Dr.Lipicky
9/30/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
9/30/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
9/30/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/1/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/1/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/2/97	Telephone Contact	AMI:Dan Cushing	FDA:Ms. K. Bongiovanni
10/2/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/2/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/6/97	FAX	FDA:Ms. K. Bongiovanni	AMI:Dan Cushing
10/6/97	Telephone Contact	AMI:Dan Cushing	FDA:Dr. Stephen B. Fredd
10/07/1997 10/10/1997	Telephone Contacts	FDA:Ms. Kathleen Bongiovanni and	AMI:Dan Cushing Cindy Lancaster Judy Molt

Date	Submission Type/Correspondence	To:	From:
10/07/1997 10/08/1997 10/09/1997	Telephone Contacts	AMI:Dan Cushing/ Kris Barone/ Cindy Lancaster/ Terry Flanagan	FDA:Dr. Lu Cui/ Dr. Anthony Proakis
10/10/97	Telephone Contact	FDA: Ms. K. Bongiovanni/ Dr. R Wolters	AMI:Dan Cushing Joanne Curley
10/10/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/13/97	Amendment to a Pending Application	FDA: Dr. Lipicky	AMI:Dan Cushing
10/15/97	Telephone Contact	FDA: Dr. Fredd/ Dr. Mahjoob	AMI:Cindy Lancaster Terry Flanagan
10/17/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/23/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/28/97	FAX	AMI:Dan Cushing	FDA: Dr. U & K.Bongiovanni
10/28/97	FAX	FDA: Dr. Khin M.U	AMI: Cindy Lancaster
10/29/97	FAX	FDA: Dr. Fredd, Dr. Mahjoob, and Ms. Kathleen Bongiovanni	AMI: Cindy Lancaster
10/29/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
10/30/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
11/6/97	Telephone Contact	FDA: Ms. K. Bongiovanni	AMI:Dan Cushing
11/7/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
11/12/97 11/19/97	Telephone Contact	AMI: Dan Cushing	FDA: Ms. Rakoff
11/12/97	FAX	FDA: Ms. K. Bongiovanni	AMI: Cindy Lancaster

Date	Submission Type/Correspondence	To:	From:
11/13/97	Telephone Contact	AMI:Dan Cushing	FDA: Dr. El-Tahtawy
11/17/97	FAX	AMI:Dan Cushing	FDA: Dr. U
11/18/97	General Correspondence	FDA:Dr. Lipicky	AMI:Dan Cushing
11/19/97	Telephone Contact	AMI: Dan Cushing	FDA: Dr. El-Tahtawy
11/19/97	FAX - Amendment to a Pending Application	FDA: Dr. Fredd & CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
11/19/97	Amendment to a Pending Application (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
11/19/97	Takeda Letter	AMI:Dan Cushing	Takeda: K. Kitazawa
11/20/97	Telephone Contact	FDA: Ms. K. Bongiovanni	AMI: Dan Cushing
11/20/97	FAX - Amendment to a Pending Application	FDA: Dr. El-Tahtawy CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
11/20/97	Amendment to a Pending Application (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
11/20/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
11/20/97	FDA Letter	AMI: Dan Cushing	FDA: R. Wolters
11/24/97	Telephone Contact	FDA: Dr. Fredd	AMI:Dan Cushing
11/25/97	Telephone Contact	AMI: Cindy Lancaster and Bob Cobuzzi	FDA: Dr. El-Tahtawy

Date	Submission Type/Correspondence	To:	From:
11/25/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
11/26/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
11/26/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/2/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/3/97	FAX - Amendment to a Pending Application: Response to FDA Questions	FDA: Dr.U CC: Kathleen Bonglovanni	AMI:Cindy Lancaster CC: Dan Cushing
12/3/97	Amendment to a Pending Application: Response to FDA Questions (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
12/5/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/8/97	Telephone Contact	AMI: Dan Cushing	FDA: Dr. El-Tahtawy
12/8/97	Telephone Contact (in response to above, 12/8/97 conversation)	FDA: Dr. El-Tahtawy	AMI: Dan Cushing AMI: Maria Sunzel
12/8/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/9/97	FAX	FDA: Dr. El-Tahtawy CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
12/10/97	FDA FAX	AMI: Cindy Lancaster	FDA: Dr. U
12/10/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/10/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/10/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/12/97	FAX	FDA: Dr. U CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
12/12/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/15/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/19/97	FAX	FDA: Dr. U CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing

Date	Submission Type/Correspondence	To:	From:
12/19/97	Amendment to a Pending Application: Response to FDA Questions (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
12/19/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/23/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
12/23/97	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/5/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/7/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/7/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/8/98	FDA FAX	AMI: Dan Cushing	FDA: Ms. K. Bonglovanni
1/9/98	FAX	FDA: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
1/9/98	Amendment to a Pending Application: Response to FDA Questions (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
1/9/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/13/98	FAX	FDA: Dr. Fredd CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
1/13/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
1/14/98	FAX	FDA: Dr. Proakis CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
1/14/98	FDA Letter	AMI: Dan Cushing	FDA: Dr. Lipicky
1/16/98	FDA FAX	AMI: Dan Cushing	FDA: Dr. Lipicky
1/23/98	Telephone Contact	AMI: Cindy Lancaster	FDA: Dr. Khim M. U.
1/23/98	Telephone Contact	FDA: Dr. Piechocki	AMI: Joanne Curley

Date	Submission Type/Correspondence	To:	From:
1/23/98	FAX	FDA: Dr. Khin M.U CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
1/26/98	Amendment to a Pending Application: Response to FDA Questions (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
2/4/98	Telephone Contact	AMI: Dan Cushing	FDA: Dr. Fredd
2/4/98	Telephone Contact	FDA: Ms. K. Bonglovanni	AMI: Dan Cushing
2/5/98	FAX	FDA: Dr. Fredd CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
2/6/98	Telephone Contact	FDA: Dr. Fredd	AMI: Terry Flanagan & Cindy Lancaster
2/12/98	FAX	FDA: Dr. Fredd CC: Ms. K. Bonglovanni	AMI: Cindy Lancaster CC: Dan Cushing
2/23/98	Telephone Contact	FDA: Dr. J. Plechocki	AMI: Joanne Curley
2/27/98	General Correspondence	FDA:Dr. Lipicky	AMI:Dan Cushing
3/10/98	FAX	AMI: Dan Cushing	FDA: K. Bonglovanni
3/10/98	Telephone Contact	AMI: Cindy Lancaster	FDA: K. Bonglovanni
3/10/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/16/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/17/98	FDA Letter (dated 3/10/98)	AMI:Dan Cushing	FDA:Dr. Lipicky
3/17/98	Telephone Contact	FDA: K. Bongiovanni	AMI: Dan Cushing
3/17/98	Telephone Contact	AMI: Dan Cushing & Denise Hardison	FDA: Dr. K. Majoob
3/19/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/19/98	FAX	FDA: K. Bonglovanni	AMI:Dan Cushing

Date	Submission Type/Correspondence	To:	From:
3/19/98	Amendment to a Pending Application: (follow-up to above fax)	FDA:Dr. Lipicky	AMI:Dan Cushing
3/20/98	Telephone Contact (2 calls)	AMI: Cindy Lancaster AMI: Dan Cushing	FDA: Dr. Khin M. U
3/20/98	FAX	FDA: K. Bongiovanni	AMI:Dan Cushing
3/20/98	FAX	FDA: Dr. Khin M. U CC: K. Bongiovanni	AMI: Cindy Lancaster CC: Dan Cushing
3/20/98	Telephone Contact	FDA: Dr. Fredd	AMI: Terry Flanagan & Cindy Lancaster
3/20/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI: Dan Cushing
3/23/98	Telephone Contact	AMI: Dan Cushing	FDA: K. Bongiovanni
3/24/98	FAX	FDA: K. Bongiovanni	AMI: Dan Cushing
3/24/98	Amendment to a Pending Application (copy of FAX)	FDA: K. Bongiovanni	AMI: Dan Cushing
3/24/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/25/98	Telephone Contact	AMI: Dan Cushing	FDA: Dr. Khin M. U
3/25/98	Amendment to a Pending Application (copy of FAX)	FDA: Dr. Khin M. U	AMI: Dan Cushing
3/25/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/25/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/25/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
3/26/98	Telephone Contact	AMI: Dan Cushing Denise Hardison Terry Flanagan	FDA: Dr. Charles Ganley
4/2/98	FAX	FDA: Dr. A. Parekh	AMI: Dan Cushing

Date	Submission Type/Correspondence	To:	From:
4/28/98	FAX (of FDA Approvable Letter)	AMI: Dan Cushing	FDA: Dr. Robert Temple via Ms. K. Bonglovanni
4/28/98	FAX	FDA: Ms. K. Bonglovann	AMI: Cindy Lancaster CC: Dan Cushing
4/28/98	FAX	FDA: Ms. K. Bonglovann	AMI: Cindy Lancaster CC: Dan Cushing
4/28/98	Amendment to a Pending Application - Response to FDA Request (follow-up to above fax)	FDA: Ms. K. Bonglovann	AMI: Dan Cushing
5/5/98	FAX	FDA: Ms. K. Bonglovann	AMI: Dan Cushing
5/6/98	FAX	FDA: Ms. K. Bonglovann	AMI: Dan Cushing
5/6/98	FAX	FDA: Ms. K. Bonglovann	AMI: Dan Cushing
5/6/98	Response to FDA Request (follow-up to above fax of 5/5/98)	FDA:Dr. Lipicky	AMI:Dan Cushing
5/7/98	FAX	FDA: Ms. K. Bonglovann	AMI: Dan Cushing
5/8/98	Response to FDA Request	FDA:Dr. Lipicky	AMI:Dan Cushing
5/12/98	Amendment to a Pending Application	FDA:Dr. Lipicky	AMI:Dan Cushing
5/18/98	Amendment to a Pending Application - Response to FDA Request	FDA:Dr. Lipicky	AMI:Dan Cushing
5/19/98	FAX - Response to FDA Request	FDA: Ms. K. Bonglovann	AMI: Cindy Lancaster CC: Dan Cushing
5/20/98	Amendment to a Pending Application - Response to FDA Request (follow-up to above fax of 5/19/98)	FDA:Dr. Lipicky	AMI:Dan Cushing
5/22/98	Amendment to a Pending Application - Response to FDA Request	FDA:Dr. Lipicky	AMI:Dan Cushing
5/22/98	Amendment to a Pending Application - Response to FDA Request	FDA:Dr. Lipicky	AMI:Dan Cushing

BRIEF DESCRIPTION OF SIGNIFICANT ACTIVITIES
DURING REGULATORY REVIEW PERIOD.

Date	Submission Type/Correspondence	Serial No.	To:	From:
05/15/1995	Original IND	000	FDA: Raymond Lipicky	AMI:Dan Cushing
05/18/1995	FDA Acknowledgment Letter		AMI	FDA: Natalia Morgenstern
06/01/1995	Information Amendment: Pharmacology/Toxicology	001	FDA: Ramond Lipicky	AMI: Elliott Berger
06/23/1995	Information Amendment: Background Information for End of Phase II Conference	002	FDA: Ramond Lipicky	AMI: Elliott Berger
07/06/1995	General Correspondence: 7/26/96 Teleconference Summary	003	FDA: Ramond Lipicky	AMI: Elliott Berger
07/07/1995	IND Safety Report - Initial Written Reports	004	FDA: Ramond Lipicky	AMI: Product Safety
07/13/1995	General Correspondence: Request for Pre-NDA Guidance	005	FDA: Ramond Lipicky	AMI: Elliott Berger
07/24/1995	IND Safety Report - Initial Written Report	006	FDA:Raymond Lipicky	AMI:Product Safety
07/24/1995	Letter from FDA		AMI: Elliott Berger	FDA: Dr. Lipicky
07/25/1995	General Correspondence: Transfer to Daniel J. Cushing	007	FDA: Ramond Lipicky	AMI: Elliott Berger
07/27/1995	Letter from FDA		AMI: Elliott Berger	FDA: Dr. Lipicky
07/27/1995	Letter from FDA		AMI: Elliott Berger	FDA: Dr. Lipicky
07/28/1995	IND Safety Report - Initial Written Report	008	FDA:Raymond Lipicky	AMI:Product Safety
08/13/1995	IND Safety Report - Follow-Up to a Written Report	009	FDA:Raymond Lipicky	AMI:Product Safety
08/17/1995	IND Safety Report - Follow-Up to a Written Report	010	FDA:Raymond Lipicky	AMI:Product Safety
08/22/1995	IND Safety Report - Initial Written Report	011	FDA:Raymond Lipicky	AMI:Product Safety
08/31/1995	Response to FDA Request for Information	012	FDA: Ramond Lipicky	AMI:Dan Cushing
09/08/1995	General Correspondence: End-Of-Phase 2 Meeting Minutes	013	FDA: Ramond Lipicky	AMI:Dan Cushing
09/12/1995	IND Safety Report - Initial Written Report & Follow-up to a Written Report	014	FDA: Ramond Lipicky	AMI:Product Safety
09/13/1995	IND Safety Report - Follow-Up to a Written Report	015	FDA: Ramond Lipicky	AMI:Product Safety
09/14/1995	Protocol Amendment: New Protocols	016	FDA: Ramond Lipicky	AMI:Dan Cushing
09/15/1995	IND Safety Report - Follow-Up to a Written Report	017	FDA: Ramond Lipicky	AMI:Product Safety

Date	Submission Type/Correspondence	Serial No.	To:	From:
09/21/1995	Letter from FDA		AMI:Dan Cushing	FDA: Natalia Morgenstern
09/26/1995	General Correspondence	018	FDA: Ramond Lipicky	AMI:Dan Cushing
09/28/1995	IND Safety Report - Follow-Up to a Written Report	019	FDA: Ramond Lipicky	AMI:Product Safety
10/12/1995	IND Safety Report - Follow-up to 2 Written Reports	020	FDA: Ramond Lipicky	AMI:Product Safety
10/13/1995	Information Amendment: CMC	021	FDA: Ramond Lipicky	AMI:Dan Cushing
10/13/1995	Letter from FDA		AMI:Dan Cushing	FDA: Dr. Lipicky
10/20/1995	General Correspondence	022	FDA: Ramond Lipicky	AMI:Dan Cushing
11/13/1995	IND Safety Report - 2 Initial Written Reports & Follow-up to a Written Report	023	FDA: Ramond Lipicky	AMI:Product Safety
11/30/1995	IND Safety Report - Initial Written Report	024	FDA: Ramond Lipicky	AMI:Product Safety
12/18/1995	IND Safety Report - Follow-Up to a Written Report	025	FDA: Ramond Lipicky	AMI:Product Safety
12/21/1995	General Correspondence: Meeting Minutes for 11/8/95 CHF Meeting	026	FDA: Ramond Lipicky	AMI:Dan Cushing
01/02/1996	IND Safety Report - Follow-Up to a Written Report	027	FDA: Ramond Lipicky	AMI:Product Safety
01/04/1996	IND Safety Report - Initial Written Report	028	FDA: Ramond Lipicky	AMI:Product Safety
01/11/1996	Protocol Amendment:Change in Protocol/New Investigators	029	FDA: Ramond Lipicky	AMI:Dan Cushing
01/11/1996	IND Safety Report - Initial Written Report	030	FDA: Ramond Lipicky	AMI:Product Safety
01/26/1996	Response to FDA Request for CMC Information	031	FDA: Ramond Lipicky	AMI:Dan Cushing
02/02/1996	Protocol Amendment: New Protocol/New Investigators	032	FDA: Ramond Lipicky	AMI:Dan Cushing
02/05/1996	IND Safety Report - Initial Written Report	033	FDA: Ramond Lipicky	AMI:Product Safety
02/08/1996	Letter from FDA		AMI:Dan Cushing	FDA: Natalia Morgenstern
02/12/1996	IND Safety Report - Initial Written Report	034	FDA: Ramond Lipicky	AMI:Product Safety
02/15/1996	Protocol Amendment: New Investigators	035	FDA: Ramond Lipicky	AMI:Dan Cushing
02/15/1996	Protocol Amendment: New Investigators	036	FDA: Ramond Lipicky	AMI:Dan Cushing
02/21/1996	Information Amendment: CMC	037	FDA: Ramond Lipicky	AMI:Dan Cushing
02/29/1996	Information Amendment: CMC	038	FDA: Ramond Lipicky	AMI:Dan Cushing

Date	Submission Type/Correspondence	Serial No.	To:	From:
03/05/1996	IND Safety Report - Follow-Up to a Written Report	039	FDA: Ramond Lipicky	AMI:Product Safety
03/08/1996	IND Safety Report - Follow-Up to a Written Report	040	FDA: Ramond Lipicky	AMI:Product Safety
03/13/1996	General Correspondence: Request for Pre-NDA CMC Guidance (stability)	041	FDA: Ramond Lipicky	AMI:Dan Cushing
03/14/1996	Protocol Amendment: Change in Protocol/New Investigators	042	FDA: Ramond Lipicky	AMI:Dan Cushing
03/26/1996	Protocol Amendment: New Investigators	043	FDA: Ramond Lipicky	AMI:Dan Cushing
03/29/1996	IND Safety Report - Follow-Up to a Written Report	044	FDA: Ramond Lipicky	AMI:Product Safety
04/01/1996	IND Safety Report - Initial Written Report	045	FDA: Ramond Lipicky	AMI:Product Safety
04/02/1996	Letter from FDA		AMI:Dan Cushing	FDA: Dr. Lipicky
04/04/1996	IND Safety Report - Initial Written Report	046	FDA: Ramond Lipicky	AMI:Product Safety
04/10/1996	Information Amendment: CMC	047	FDA: Ramond Lipicky	AMI:Dan Cushing
04/11/1996	Protocol Amendment: New Protocol/New Investigators	048	FDA: Ramond Lipicky	AMI:Dan Cushing
04/24/1996	Information Amendment: CMC	049	FDA: Ramond Lipicky	AMI:Dan Cushing
05/01/1996	Protocol Amendment: Change in Protocol/New Investigators	050	FDA: Ramond Lipicky	AMI:Dan Cushing
05/07/1996	IND Safety Report - Initial Written Report & Follow-up to a Written Report	051	FDA: Ramond Lipicky	AMI:Product Safety
05/08/1996	IND Safety Report - Follow-Up to a Written Report	052	FDA: Ramond Lipicky	AMI:Product Safety
05/08/1996	Information Amendment: CMC	053	FDA: Ramond Lipicky	AMI:Dan Cushing
05/17/1996	Protocol Amendment: New Investigators	054	FDA: Ramond Lipicky	AMI:Dan Cushing
05/23/1996	Protocol Amendment: New Investigators	055	FDA: Ramond Lipicky	AMI:Dan Cushing
05/23/1996	Protocol Amendment: New Investigators	056	FDA: Ramond Lipicky	AMI:Dan Cushing
05/23/1996	Protocol Amendment: New Investigators	057	FDA: Ramond Lipicky	AMI:Dan Cushing
05/24/1996	IND Safety Report - Follow-Up to a Written Report	058	FDA: Ramond Lipicky	AMI:Product Safety
05/28/1996	IND Safety Report - Initial Written Report	059	FDA: Ramond Lipicky	AMI:Product Safety
05/30/1996	IND Safety Report - Follow-Up to a Written Report	060	FDA: Ramond Lipicky	AMI:Product Safety

Date	Submission Type/Correspondence	Serial No.	To:	From:
06/06/1996	IND Safety Report - Follow-Up to a Written Report	061	FDA: Ramond Lipicky	AMI:Product Safety
06/10/1996	IND Safety Report - Follow-Up to a Written Report	062	FDA: Ramond Lipicky	AMI:Product Safety
06/11/1996	IND Safety Report - Follow-Up to a Written Report	063	FDA: Ramond Lipicky	AMI:Product Safety
06/26/1996	IND Safety Report - Initial Written Report	064	FDA: Ramond Lipicky	AMI:Product Safety
07/12/1996	IND Safety Report - Follow-Up to a Written Report	065	FDA: Ramond Lipicky	AMI:Product Safety
07/15/1996	Protocol Amendment: New Investigators	066	FDA: Ramond Lipicky	AMI:Dan Cushing
07/16/1996	Protocol Amendment: New Investigators	067	FDA: Ramond Lipicky	AMI:Dan Cushing
07/22/1996	Protocol Amendment: New Investigators	068	FDA: Ramond Lipicky	AMI:Dan Cushing
07/31/1996	IND Safety Report - Follow-Up to a Written Report	069	FDA: Ramond Lipicky	AMI:Product Safety
08/02/1996	IND Annual Report	070	FDA: Ramond Lipicky	AMI:Dan Cushing
08/13/1996	Protocol Amendment: New Investigators	071	FDA: Ramond Lipicky	AMI:Dan Cushing
08/13/1996	IND Safety Report - Initial Written Report	072	FDA: Ramond Lipicky	AMI:Product Safety
08/22/1996	Protocol Amendment: New Investigator	073	FDA: Ramond Lipicky	AMI:Dan Cushing
09/26/1996	Information Amendment: CMC	074	FDA: Ramond Lipicky	AMI:Dan Cushing
10/07/1996	Protocol Amendment: New Investigators	075	FDA: Ramond Lipicky	AMI:Dan Cushing
10/07/1996	IND Safety Report - Initial Written Report & Follow-up to a Written Report	076	FDA: Ramond Lipicky	AMI:Product Safety
10/08/1996	IND Safety Report - Follow-Up to a Written Report	077	FDA: Ramond Lipicky	AMI:Product Safety
10/11/1996	IND Safety Report - Follow-Up to a Written Report	078	FDA: Ramond Lipicky	AMI:Product Safety
10/16/1996	General Correspondence: Pre-NDA Conference Background Package	079	FDA: Ramond Lipicky	AMI:Dan Cushing
10/18/1996	IND Safety Report - Follow-Up to a Written Report	080	FDA: Ramond Lipicky	AMI:Product Safety
11/04/1996	IND Safety Report - Follow-Up to a Written Report	081	FDA: Ramond Lipicky	AMI:Product Safety
11/12/1996	Telephone Contact		AMI: Dan Cushing	FDA: Ms. K. Bongiovanni Dr. F. Zielinski
11/21/1996	IND Safety Report - Follow-Up to a Written Report	082	FDA: Ramond Lipicky	AMI:Product Safety
11/27/1996	IND Safety Report - Follow-Up to a Written Report	083	FDA: Ramond Lipicky	AMI:Product Safety

Date	Submission Type/Correspondence	Serial No.	To:	From:
12/02/1996	Letter from FDA		AMI:Dan Cushing	FDA: Natalia Morgenstern
12/02/1996	Letter from FDA		AMI:Dan Cushing	FDA: Natalia Morgenstern
12/03/1996	FAX		FDA: Kathleen Bongiovanni	AMI:Dan Cushing
12/11/1996	General Correspondence: Validation of Dissolution Test Conditions	084	FDA: Ramond Lipicky	AMI:Dan Cushing
12/18/1996	General Correspondence	085	FDA: Ramond Lipicky	AMI:Dan Cushing
01/15/1997	Letter from FDA		AMI:Dan Cushing	FDA: Dr. Lipicky
01/21/1997	General Correspondence	086	FDA: Dr. Lipicky	AMI:Dan Cushing
01/27/1997	Telephone Contact		AMI:Dan Cushing	FDA:K. Bongiovanni
01/29/1997	Telephone Contact		AMI:Don Dwyer	FDA:A. Elhage
02/03/1997	Telephone Contact		FDA:Jeanna Johnson	AMI:Don Dwyer
02/12/1997	Information Amendment: Pharmacology/Toxicology	087	FDA: Ramond Lipicky	AMI:Dan Cushing
02/12/1997	General Correspondence: Request for Waiver	088	FDA: Ramond Lipicky	AMI:Dan Cushing
02/14/1997	Information Amendment: Clinical	089	FDA:Raymond Lipicky	AMI:Dan Cushing
02/19/1997	Other - Approval Sheet			
02/20/1997	Letter from FDA		AMI:Dan Cushing	FDA: Janet Wookcock
02/21/1997	FAX		AMI:Dan Cushing	FDA: Janet Woodcock
02/25/1997	IND Safety Report - Initial Written Report	090	FDA:Raymond Lipicky	AMI:Product Safety and Epidemiology
03/04/1997	IND Safety Report - Initial Written Report	091	FDA:Raymond Lipicky	AMI:Product Safety and Epidemiology
03/12/1997	Letter from FDA		AMI:Dan Cushing	FDA:Raymond Lipicky
03/28/1997	Information Amendment - CMC	092	FDA:Raymond Lipicky	AMI:Dan Cushing
03/28/1997	Other - Approval Sheet			
04/04/1997	Protocol Amendment: New Protocol/New Investigator	093	FDA:Raymond Lipicky	AMI:Dan Cushing
04/08/1997	Protocol Amendment: New Protocol	094	FDA:Raymond Lipicky	AMI:Dan Cushing
04/09/1997	General Correspondence	095	FDA:Raymond Lipicky	AMI:Dan Cushing
04/14/1997	Telephone Contact		AMI:Dan Cushing	FDA:M. Gordon
04/22/1997	Telephone Contact		AMI:Don Dwyer	FDA:K. Bongiovanni

Date	Submission Type/Correspondence	Serial No.	To:	From:
05/15/1997	IND Safety Report - Follow-Up to a Written Report	096	FDA:Raymond Lipicky	AMI:Product Safety
05/23/1997	IND Safety Report - Initial Written Report	097	FDA:Raymond Lipicky	AMI:Product Safety
06/03/1997	Information Amendment: CMC	098	FDA:Raymond Lipicky	AMI:Dan Cushing
06/26/1997	IND Safety Report - Follow-Up to a Written Report	099	FDA:Raymond Lipicky	AMI:Product Safety
06/27/1997	Information Amendment: CMC	100	FDA:Raymond Lipicky	AMI:Dan Cushing
07/08/1997	IND Safety Report - Follow-Up to a Written Report	101	FDA:Raymond Lipicky	AMI:Product Safety
07/11/1997	IND Safety Report - Follow-Up to a Written Report	102	FDA:Raymond Lipicky	AMI:Product Safety
07/16/1997	Information Amendment: CMC	103	FDA:Raymond Lipicky	AMI:Dan Cushing
07/21/1997	IND Safety Report - Follow-Up to a Written Report	104	FDA:Raymond Lipicky	AMI:Product Safety
07/24/1997	Telephone Contact		AMI:Robert Cobuzzi	FDA: Dr. Ahmed El Tahtawy
07/25/1997	Telephone Contact		AMI:Dan Cushing trans. to: Robert Cobuzzi/ Terry Flanagan	FDA:Dr. Steve Caras
07/28/1997	Telephone Contact		AMI:Robert Cobuzzi/ Terry Flanagan	FDA:Dr. Steve Caras
08/18/1997	IND Safety Report - Follow-Up to a Written Report	105	FDA:Raymond Lipicky	AMI:Product Safety
08/25/1997	Protocol Amendment: Change in Protocol / New Investigators	106	FDA:Raymond Lipicky	AMI:Dan Cushing
08/28/1997	Protocol Amendment: New Protocol	107	FDA:Raymond Lipicky	AMI:Dan Cushing
09/09/1997	Telephone Contact	107	AMI:Dan Cushing	FDA:Dr. Stephen B. Fredd
09/22/1997	IND Annual Report	108	FDA:Raymond Lipicky	AMI:Dan Cushing
09/26/1997	Protocol Amendment: New Investigators	109	FDA:Raymond Lipicky	AMI:Dan Cushing
09/26/1997	Protocol Amendment: New Investigators	110	FDA:Raymond Lipicky	AMI:Dan Cushing
10/01/1997	Information Amendment: Clinical	111	FDA:Raymond Lipicky	AMI:Dan Cushing
10/13/1997	Information Amdndment: CMC	112	FDA:Raymond Lipicky	AMI:Dan Cushing
10/16/1997	Protocol Amendment: New Investigators	113	FDA:Raymond Lipicky	AMI:Dan Cushing

Date	Submission Type/Correspondence	Serial No.	To:	From:
10/20/1997	Protocol Amendment - New Investigators/ Additional Investigator Information	114	FDA:Raymond Lipicky	AMI:Dan Cushing
10/23/1997	Protocol Amendment - New Investigators/ Additional Investigator Information	115	FDA:Raymond Lipicky	AMI:Dan Cushing
10/29/1997	IND Safety Report - Follow-Up to a Written Report	116	FDA:Raymond Lipicky	AMI:Product Safety
11/06/1997	IND Safety Report - Initial Written Report	117	FDA:Raymond Lipicky	AMI:Product Safety
11/11/1997	Protocol Amendment: New Investigators/Additional Investigator Information	118	FDA:Raymond Lipicky	AMI:Dan Cushing
11/26/1997	IND Safety Report - Initial Written Report	119	FDA:Raymond Lipicky	AMI:Product Safety
12/04/1997	IND Safety Report - Initial Written Report	120	FDA:Raymond Lipicky	AMI:Product Safety
12/05/1997	Protocol Amendment: New Investigators/Additional Investigator Information	121	FDA:Raymond Lipicky	AMI:Dan Cushing
12/09/1997	IND Safety Report - Follow-Up to a Written Report	122	FDA:Raymond Lipicky	AMI:Product Safety
12/10/1997	IND Safety Report - Follow-Up to a Written Report	123	FDA:Raymond Lipicky	AMI:Product Safety
12/16/1997	IND Safety Report - Follow-Up to a Written Report	124	FDA:Raymond Lipicky	AMI:Product Safety
12/17/1997	Protocol Amendment: New Investigators/Additional Investigator Information	125	FDA:Raymond Lipicky	AMI:Dan Cushing
12/22/1997	Protocol Amedment: New Protocol/New Investigator/Label Copy	126	FDA:Raymond Lipicky	AMI:Dan Cushing
12/22/1997	IND Safety Report - Follow-Up to a Written Report	127	FDA:Raymond Lipicky	AMI:Product Safety
12/30/1997	IND Safety Report - Follow-Up to a Written Report	128	FDA:Raymond Lipicky	AMI:Product Safety
01/12/1998	Protocol Amendment: New Investigators/Additional Investigator Information	129	FDA:Raymond Lipicky	AMI:Dan Cushing
01/14/1998	FDA Letter		AMI: Dan Cushing	FDA: Dr. Lipicky
01/16/1998	Protocol Amendment: New Protocol	130	FDA:Raymond Lipicky	AMI:Dan Cushing
01/19/1998	IND Safety Report - Follow-Up to a Written Report	131	FDA:Raymond Lipicky	AMI:Product Safety
01/22/1998	IND Safety Report - Follow-Up to a Written Report	132	FDA:Raymond Lipicky	AMI:Product Safety
02/03/1998	IND Safety Report - Follow-Up to a Written Report	133	FDA:Raymond Lipicky	AMI:Product Safety
02/05/1998	IND Safety Report - Follow-Up to a Written Report	134	FDA:Raymond Lipicky	AMI:Product Safety

Date	Submission Type/Correspondence	Serial No.	To:	From:
02/18/1998	Protocol Amendment: Additional Investigator Information	135	FDA:Raymond Lipicky	AMI:Dan Cushing
02/19/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	136	FDA:Raymond Lipicky	AMI:Product Safety
02/20/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	137	FDA:Raymond Lipicky	AMI:Product Safety
02/23/1998	General Correspondence	138	FDA:Raymond Lipicky	AMI:Dan Cushing
02/23/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	139	FDA:Raymond Lipicky	AMI:Product Safety
02/24/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	140	FDA:Raymond Lipicky	AMI:Product Safety
02/26/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	141	FDA:Raymond Lipicky	AMI:Product Safety
02/27/1998	IND Safety Report - Initial Written Report (Primary)	142	FDA:Raymond Lipicky	AMI:Product Safety
03/02/1998	IND Safety Report - Follow-Up to a Written Report (primary)	143	FDA:Raymond Lipicky	AMI:Product Safety
03/03/1998	IND Safety Report - Initial Written Report (cross-reference)	144	FDA:Raymond Lipicky	AMI:Product Safety
03/05/1998	Protocol Amendment: Change in Protocol	145	FDA:Raymond Lipicky	AMI:Dan Cushing
03/10/1998	IND Safety Report - Initial Written Report (Primary)	146	FDA:Raymond Lipicky	AMI:Product Safety
03/12/1998	Protocol Amendment: New Investigators	147	FDA:Raymond Lipicky	AMI:Dan Cushing
03/18/1998	IND Safety Report - Follow-Up to a Written Report (primary)	148	FDA:Raymond Lipicky	AMI:Product Safety
03/20/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	149	FDA:Raymond Lipicky	AMI:Product Safety
03/23/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	150	FDA:Raymond Lipicky	AMI:Product Safety
03/23/1998	IND Safety Report - Initial Written Report (Primary)	151	FDA:Raymond Lipicky	AMI:Product Safety
03/24/1998	Protocol Amendment: Change in Protocol	152	FDA:Raymond Lipicky	AMI:Dan Cushing
03/27/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	153	FDA:Raymond Lipicky	AMI:Product Safety
03/30/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	154	FDA:Raymond Lipicky	AMI:Product Safety
04/08/1998	Information Amendment - CMC	155	FDA:Raymond Lipicky	AMI:Dan Cushing
04/08/1998	Protocol Amendment: Change in Protocol	156	FDA:Raymond Lipicky	AMI:Dan Cushing
04/08/1998	IND Safety Report - Follow-Up to a Written Report (primary)	157	FDA:Raymond Lipicky	AMI:Product Safety
04/08/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	158	FDA:Raymond Lipicky	AMI:Product Safety

Date	Submission Type/Correspondence	Serial No.	To:	From:
04/09/1998	Protocol Amendment: New Investigator/ Additional Investigator Information	159	FDA:Raymond Lipicky	AMI:Dan Cushing
04/10/1998	IND Safety Report - Follow-Up to a Written Report (primary)	160	FDA:Raymond Lipicky	AMI:Product Safety
04/16/1998	Information Amendment - CMC	161	FDA:Raymond Lipicky	AMI:Dan Cushing
04/17/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	162	FDA:Raymond Lipicky	AMI:Product Safety
04/23/1998	Protocol Amendment: New Protocol	163	FDA:Raymond Lipicky	AMI:Dan Cushing
04/23/1998	IND Safety Report - Follow-Up to a Written Report (primary)	164	FDA:Raymond Lipicky	AMI:Product Safety
04/27/1998	IND Safety Report - 2 Initial and 1 Follow-Up to a Written Report (primary reports)	165	FDA:Raymond Lipicky	AMI:Product Safety
04/27/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	166	FDA:Raymond Lipicky	AMI:Product Safety
04/30/1998	IND Safety Report - Initial Written Report (Primary)	167	FDA:Raymond Lipicky	AMI:Product Safety
05/08/1998	Protocol Amendment: New Investigators	168	FDA:Raymond Lipicky	AMI:Dan Cushing
05/11/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	169	FDA:Raymond Lipicky	AMI:Product Safety
05/12/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	170	FDA:Raymond Lipicky	AMI:Product Safety
05/12/1998	IND Safety Report - Initial Written Report (Primary)	171	FDA:Raymond Lipicky	AMI:Product Safety
05/13/1998	IND Safety Report - Initial Written Report (Primary)	172	FDA:Raymond Lipicky	AMI:Product Safety
05/14/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	173	FDA:Raymond Lipicky	AMI:Product Safety
05/14/1998	Telephone Contact		FDA: Dr. Khin U	AMI: Dan Cushing
05/15/1998	IND Safety Report - 1 Initial and 2 Follow-Ups to Written Reports (primary reports)	174	FDA:Raymond Lipicky	AMI:Product Safety
05/19/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	175	FDA:Raymond Lipicky	AMI:Product Safety
05/20/1998	IND Safety Report - Follow-Up to a Written Report (primary)	176	FDA:Raymond Lipicky	AMI:Product Safety
05/22/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	177	FDA:Raymond Lipicky	AMI:Product Safety
06/01/1998	Protocol Amendment: Change in Protocol	178	FDA:Raymond Lipicky	AMI:Dan Cushing
06/01/1998	IND Safety Report - Initial & Follow-Up to Written Reports (primary)	179	FDA:Raymond Lipicky	AMI:Product Safety
06/01/1998	IND Safety Report - Follow-Up to a Written Report (cross-reference)	180	FDA:Raymond Lipicky	AMI:Product Safety

DATE 10-6-08 APPLICATION NUMBER 07/681238

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#18

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 5,196,444 was filed on July 22, 1998, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application, ATACAND™ (candesartan cilexetil), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (703) 306-3159 (telephone) or (703)308-6916 (facsimile).

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Patricia D. Granados
Foley & Lardner
Washington Harbour, Suite 500
3000 K Street, N.W.
Washington DC 20007-5109

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